=> fil reg; d stat que l8
FILE 'REGISTRY' ENTERED AT 12:38:05 ON 10 APR 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 9 APR 2003 HIGHEST RN 502545-60-0
DICTIONARY FILE UPDATES: 9 APR 2003 HIGHEST RN 502545-60-0

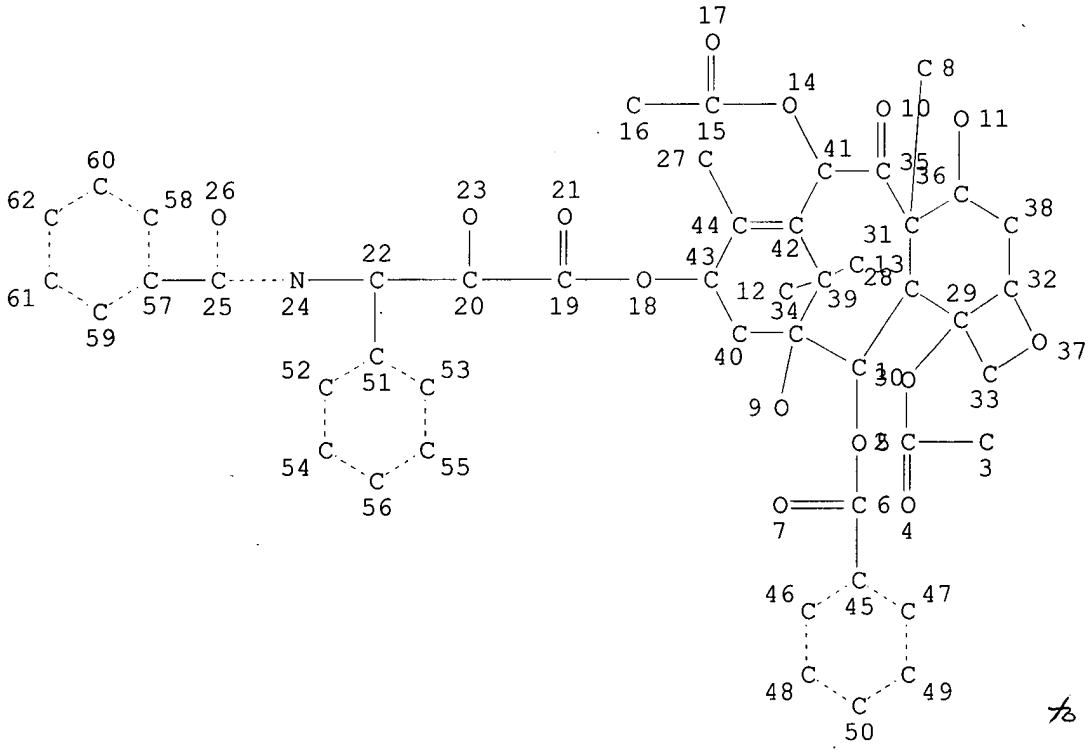
TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L6 STR



family search done to retrieve salts, stereoisomers, isotopically labelled substances & multicomponent substances

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

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L8          71 SEA FILE=REGISTRY FAM FUL L6

100.0% PROCESSED   1348 ITERATIONS                    71 ANSWERS
SEARCH TIME: 00.00.01


=> fil capl; d que nos l23; d que nos l28; d que nos l34

FILE 'CAPLUS' ENTERED AT 12:38:05 ON 10 APR 2003
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FILE COVERS 1907 - 10 Apr 2003  VOL 138 ISS 15
FILE LAST UPDATED: 9 Apr 2003  (20030409/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L6              STR
L8           71 SEA FILE=REGISTRY FAM FUL L6
L9            1 SEA FILE=REGISTRY ABB=ON  ETHANOL/CN
L10           1 SEA FILE=REGISTRY ABB=ON  CITRIC ACID/CN
L11           1 SEA FILE=REGISTRY ABB=ON  ACETIC ACID/CN
L12          20 SEA FILE=REGISTRY ABB=ON  CASTOR OIL, ETHOXYLATED?/CN
L13        7488 SEA FILE=CAPLUS ABB=ON  (PACLITAXEL OR TAXOL)/OBI
L14        6976 SEA FILE=CAPLUS ABB=ON  L8
L15      191380 SEA FILE=CAPLUS ABB=ON  L9 OR (ETHANOL OR ETOH OR ETHYL
                ALCOHOL)/OBI
L16       46244 SEA FILE=CAPLUS ABB=ON  L10 OR (CITRIC ACID)/OBI
L17      147274 SEA FILE=CAPLUS ABB=ON  L11 OR ACETIC ACID/OBI
L18           1 SEA FILE=REGISTRY ABB=ON  CASTOR OIL/CN
L19        2891 SEA FILE=CAPLUS ABB=ON  (L18 OR CASTOR OIL/CT)(L)?ETHOXYLAT?
L20          43 SEA FILE=CAPLUS ABB=ON  L12
L23          10 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND (L19 OR L20) AND (L16
                OR L17) AND L15


L6              STR
L8           71 SEA FILE=REGISTRY FAM FUL L6
L9            1 SEA FILE=REGISTRY ABB=ON  ETHANOL/CN
L10           1 SEA FILE=REGISTRY ABB=ON  CITRIC ACID/CN
L11           1 SEA FILE=REGISTRY ABB=ON  ACETIC ACID/CN
L12          20 SEA FILE=REGISTRY ABB=ON  CASTOR OIL, ETHOXYLATED?/CN
L13        7488 SEA FILE=CAPLUS ABB=ON  (PACLITAXEL OR TAXOL)/OBI
L14        6976 SEA FILE=CAPLUS ABB=ON  L8
L15      191380 SEA FILE=CAPLUS ABB=ON  L9 OR (ETHANOL OR ETOH OR ETHYL
                ALCOHOL)/OBI
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L16        46244 SEA FILE=CAPLUS ABB=ON  L10 OR (CITRIC ACID)/OBI
L17       147274 SEA FILE=CAPLUS ABB=ON  L11 OR ACETIC ACID/OBI
L18            1 SEA FILE=REGISTRY ABB=ON  CASTOR OIL/CN
L19         2891 SEA FILE=CAPLUS ABB=ON  (L18 OR CASTOR OIL/CT)(L)?ETHOXYLAT?
L20           43 SEA FILE=CAPLUS ABB=ON  L12
L26        50056 SEA FILE=CAPLUS ABB=ON  STOR?(5A)STAB?
L28            4 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND L26 AND ((L15 OR L16
                 OR L17) OR (L19 OR L20))


L6               STR
L8            71 SEA FILE=REGISTRY FAM FUL L6
L9             1 SEA FILE=REGISTRY ABB=ON  ETHANOL/CN
L10            1 SEA FILE=REGISTRY ABB=ON  CITRIC ACID/CN
L11            1 SEA FILE=REGISTRY ABB=ON  ACETIC ACID/CN
L12           20 SEA FILE=REGISTRY ABB=ON  CASTOR OIL, ETHOXYLATED?/CN
L13         7488 SEA FILE=CAPLUS ABB=ON  (PACLITAXEL OR TAXOL)/OBI
L14         6976 SEA FILE=CAPLUS ABB=ON  L8
L15       191380 SEA FILE=CAPLUS ABB=ON  L9 OR (ETHANOL OR ETOH OR ETHYL
                 ALCOHOL)/OBI
L16        46244 SEA FILE=CAPLUS ABB=ON  L10 OR (CITRIC ACID)/OBI
L17       147274 SEA FILE=CAPLUS ABB=ON  L11 OR ACETIC ACID/OBI
L18            1 SEA FILE=REGISTRY ABB=ON  CASTOR OIL/CN
L19         2891 SEA FILE=CAPLUS ABB=ON  (L18 OR CASTOR OIL/CT)(L)?ETHOXYLAT?
L20           43 SEA FILE=CAPLUS ABB=ON  L12
L29         7692 SEA FILE=CAPLUS ABB=ON  STABILIZING AGENTS/CT
L30       124431 SEA FILE=CAPLUS ABB=ON  DRUG DELIVERY SYSTEMS+OLD/CT
L34            7 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND L29 AND ((L15 OR L16
                 OR L17) OR (L19 OR L20)) AND L30


=> s l23 or l28 or l34

L130          17 L23 OR L28 OR L34

=> fil medl; d que l59; d que l60; d que l65

FILE 'MEDLINE' ENTERED AT 12:38:07 ON 10 APR 2003

 FILE LAST UPDATED: 9 APR 2003 (20030409/UP).  FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/summ2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L53          416 SEA FILE=MEDLINE ABB=ON  CASTOR OIL/CT
L59            3 SEA FILE=MEDLINE ABB=ON  L50 AND L53


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L51         4122 SEA FILE=MEDLINE ABB=ON  CITRIC ACID/CT
L52         3074 SEA FILE=MEDLINE ABB=ON  ACETIC ACID/CT
L60            1 SEA FILE=MEDLINE ABB=ON  L50 AND (L51 OR L52)
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L50        7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L54       45703 SEA FILE=MEDLINE ABB=ON  ETHANOL/CT
L62       24525 SEA FILE=MEDLINE ABB=ON  L54(L)(PD OR AD OR PK OR TU)/CT
L64         383 SEA FILE=MEDLINE ABB=ON  CREMOPHOR EL
L65           5 SEA FILE=MEDLINE ABB=ON  L50 AND L62 AND L64
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Subheadings
PD - pharmacology
AD - administration & dosage
PK - pharmacokinetics
TU - Therapeutic use

```
=> s l59 or l60 or l65

L131          9 L59 OR L60 OR L65

=> fil embase

FILE 'EMBASE' ENTERED AT 12:38:08 ON 10 APR 2003
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 FILE COVERS 1974 TO 3 Apr 2003 (20030403/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l85

L70        2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L71       76078 SEA FILE=EMBASE ABB=ON  ALCOHOL/CT
L74         137 SEA FILE=EMBASE ABB=ON  RICINOMACROGOL/CT
L75         893 SEA FILE=EMBASE ABB=ON  CASTOR OIL/CT
L76         728 SEA FILE=EMBASE ABB=ON  CREMOPHOR/CT
L82       81481 SEA FILE=EMBASE ABB=ON  "CARBOXYLIC ACIDS AND THEIR DERIVATIVES
                "+NT/CT
L85           2 SEA FILE=EMBASE ABB=ON  L70 AND (L74 OR L75 OR L76) AND (L82
                OR L71)


=> fil drugu; d que l96; d que l97; d que l112

FILE 'DRUGU' ENTERED AT 12:38:09 ON 10 APR 2003
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FILE LAST UPDATED: 8 APR 2003       <20030408/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L90        6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L91      166684 SEA FILE=DRUGU ABB=ON  ACID#
L93        1316 SEA FILE=DRUGU ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                CREMOPHOR
L94        2445 SEA FILE=DRUGU ABB=ON  ETHANOL/CT
L96           0 SEA FILE=DRUGU ABB=ON  L90 AND L91 AND L93 AND L94
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L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L91       166684 SEA FILE=DRUGU ABB=ON  ACID#
L92         7449 SEA FILE=DRUGU ABB=ON  (CITRIC OR ACETIC)(W)L91
L93         1316 SEA FILE=DRUGU ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L97            0 SEA FILE=DRUGU ABB=ON  L90 AND L93 AND L92



L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L91       166684 SEA FILE=DRUGU ABB=ON  ACID#
L92         7449 SEA FILE=DRUGU ABB=ON  (CITRIC OR ACETIC)(W)L91
L93         1316 SEA FILE=DRUGU ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L94         2445 SEA FILE=DRUGU ABB=ON  ETHANOL/CT
L98        11741 SEA FILE=DRUGU ABB=ON  STOR###
L99        70702 SEA FILE=DRUGU ABB=ON  STAB?
L111           9 SEA FILE=DRUGU ABB=ON  L90 AND (L91 OR L92 OR L93 OR L94) AND
                 L98 AND L99
L112           8 SEA FILE=DRUGU ABB=ON  L111 NOT (STORY OR STORIES OR STORIED)


=> fil wpids; d que l120

FILE 'WPIDS' ENTERED AT 12:38:10 ON 10 APR 2003
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FILE LAST UPDATED:          7 APR 2003      <20030407/UP>
MOST RECENT DERWENT UPDATE:     200323        <200323/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L113        1452 SEA FILE=WPIDS ABB=ON  PACLITAXEL OR TAXOL
L114       62094 SEA FILE=WPIDS ABB=ON  ETHANOL OR ETOH OR ETHYL ALCOHOL
L115      813664 SEA FILE=WPIDS ABB=ON  ACID#
L116       50315 SEA FILE=WPIDS ABB=ON  (CITRIC OR ACETIC)(W)L115
L117        5677 SEA FILE=WPIDS ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L120           5 SEA FILE=WPIDS ABB=ON  L113 AND L116 AND L117 AND L114


=> dup rem l131,l112,l130,185,l120
FILE 'MEDLINE' ENTERED AT 12:39:12 ON 10 APR 2003

FILE 'DRUGU' ENTERED AT 12:39:12 ON 10 APR 2003
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FILE 'CAPLUS' ENTERED AT 12:39:12 ON 10 APR 2003
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FILE 'EMBASE' ENTERED AT 12:39:12 ON 10 APR 2003

FILE 'WPIDS' ENTERED AT 12:39:12 ON 10 APR 2003

PROCESSING COMPLETED FOR L131
PROCESSING COMPLETED FOR L112
PROCESSING COMPLETED FOR L130
PROCESSING COMPLETED FOR L85
PROCESSING COMPLETED FOR L120
L132 38 DUP REM L131 L112 L130 L85 L120 (3 DUPLICATES REMOVED)
ANSWERS '1-9' FROM FILE MEDLINE
ANSWERS '10-17' FROM FILE DRUGU
ANSWERS '18-34' FROM FILE CAPLUS
ANSWER '35' FROM FILE EMBASE
ANSWERS '36-38' FROM FILE WPIDS

=> d ibib ab hitrn 1-38

L132 ANSWER 1 OF 38 MEDLINE
ACCESSION NUMBER: 2002276315 MEDLINE
DOCUMENT NUMBER: 22000994 PubMed ID: 12006516
TITLE: Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel.
AUTHOR: Ibrahim Nuhad K; Desai Neil; Legha Sewa; Soon-Shiong Patrick; Theriault Richard L; Rivera Edgardo; Esmaeli Bita; Ring Sigrid E; Bedikian Agop; Hortobagyi Gabriel N; Ellerhorst Julie A
CORPORATE SOURCE: Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.
SOURCE: CLINICAL CANCER RESEARCH, (2002 May) 8 (5) 1038-44. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020518
Last Updated on STN: 20021018
Entered Medline: 20021017

AB PURPOSE: ABI-007 is a novel Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. The absence of Cremophor EL may permit ABI-007 to be administered without the premedications used routinely for the prevention of hypersensitivity reactions. Furthermore, this novel formulation permits a higher paclitaxel concentration in solution and, thus, a decreased infusion volume and time. This Phase I study examines the toxicity profile, maximum tolerated dose (MTD), and pharmacokinetics of ABI-007. EXPERIMENTAL DESIGN: ABI-007 was administered in the outpatient setting, as a 30-min infusion without premedications. Doses of ABI-007 ranged from 135 (level 0) to 375 mg/m2 (level 3). Sixteen patients participated in pharmacokinetic studies. RESULTS: Nineteen patients were treated. No acute hypersensitivity reactions were observed during the infusion period. Hematological toxicity was mild and not cumulative. Dose-limiting toxicity, which occurred in 3 of 6 patients treated at level 3 (375 mg/m2), consisted of sensory neuropathy (3 patients), stomatitis (2 patients), and superficial keratopathy (2 patients). The MTD was thus determined to be 300 mg/m2 (level 2).

Pharmacokinetic analyses revealed paclitaxel C(max) and area under the curve(inf) values to increase linearly over the ABI-007 dose range of 135-300 mg/m2. C(max) and area under the curve(inf) values for individual patients correlated well with toxicity. CONCLUSIONS: ABI-007 offers several features of clinical interest, including rapid infusion rate, absence of requirement for premedication, and a high paclitaxel MTD. Our results provide support for Phase II trials to determine the antitumor activity of this drug.

L132 ANSWER 2 OF 38 MEDLINE
ACCESSION NUMBER: 2001699031 MEDLINE
DOCUMENT NUMBER: 21610136 PubMed ID: 11745194
TITLE: Intraarterial chemotherapy with polyoxyethylated castor oil free paclitaxel, incorporated in albumin nanoparticles (ABI-007): Phase II study of patients with squamous cell carcinoma of the head and neck and anal canal: preliminary evidence of clinical activity.
AUTHOR: Damascelli B; Cantu G; Mattavelli F; Tamplenizza P; Bidoli P; Leo E; Dosio F; Cerrotta A M; Di Tolla G; Frigerio L F; Garbagnati F; Lanocita R; Marchiano A; Patelli G; Spreafico C; Ticha V; Vespro V; Zunino F
CORPORATE SOURCE: Department of Radiology, Istituto Nazionale Tumori, Milano, Italy.. damascelli@istitutotumori.mi.it
SOURCE: CANCER, (2001 Nov 15) 92 (10) 2592-602.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011219
Last Updated on STN: 20020125
Entered Medline: 20020104

AB BACKGROUND: This study was designed to determine the feasibility, maximum tolerated dose, and toxicities of intraarterial administration of paclitaxel-albumin nanoparticles in patients with advanced head and neck and recurrent anal canal squamous cell carcinoma. Antitumor activity also was assessed. METHODS: Forty-three patients (31 with advanced head and neck and 12 with recurrent anal canal squamous cell carcinoma) were treated intraarterially with ABI-007 every 4 weeks for 3 cycles. In total, 120 treatment cycles were completed, 86 in patients with head and neck carcinoma (median, 3 cycles; range, 1-4) and 34 in patients with anal canal carcinoma (median, 3 cycles; range, 1-4). ABI-007 was compared preliminarily with Taxol for in vitro cytostatic activity. Increasing dose levels from 120 to 300 mg/m2 were studied in 18 patients. Pharmacokinetic profiles after intraarterial administration were obtained in a restricted number of patients. RESULTS: The dose-limiting toxicity of ABI-007 was myelosuppression consisting of Grade 4 neutropenia in 3 patients. Nonhematologic toxicities included total alopecia (30 patients), gastrointestinal toxicity (3 patients, Grade 2), skin toxicity (5 patients, Grade 2), neurologic toxicity (4 patients, Grade 2) ocular toxicity (1 patient, Grade 2), flu-like syndrome (7 patients, Grade 2; 1 patient, Grade 3). In total, 120 transfemoral, percutaneous catheterization procedure-related complications occurred only during catheterization of the neck vessels in 3 patients (2 TIA, 1 hemiparesis) and resolved spontaneously. CONCLUSIONS: Intraarterial administration of ABI-007 by percutaneous catheterization does not require premedication, is easy and reproducible, and has acceptable toxicity. The maximum tolerated dose in a single administration was 270 mg/m2. Most dose levels showed considerable antitumor activity (42 assessable patients with 80.9% complete response and partial response). The recommended Phase II dose is

230 mg/m2 every 3 weeks.

L132 ANSWER 3 OF 38 MEDLINE
ACCESSION NUMBER: 2001217067 MEDLINE
DOCUMENT NUMBER: 21134777 PubMed ID: 11237379
TITLE: Phase I trial and pharmacological study of a 3-hour paclitaxel infusion in children with refractory solid tumours: a SFOP study.
AUTHOR: Doz F; Gentet J C; Pein F; Frappaz D; Chastagner P; Moretti S; Vassal G; Arditti J; Tellingen O V; Iliadis A; Catalin J
CORPORATE SOURCE: Departement d'Oncologie Pediatrique, Institut Curie, 26 rue d'Ulm, Paris, 75231 Cx 05, France.
SOURCE: BRITISH JOURNAL OF CANCER, (2001 Mar 2) 84 (5) 604-10.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB The maximum tolerated dose of paclitaxel administered by 24-hour continuous infusion in children is known. Short infusion might offer equivalent antitumour efficacy and reduced haematological toxicity, without increasing the allergic risk. Our aims were to determine the maximum tolerated dose and the pharmacokinetics of paclitaxel in children when administered in 3-h infusion every 3 weeks. Patients older than 6 months, younger than 20 years with refractory malignant solid tumours were eligible when they satisfied standard haematological, renal, hepatic and cardiologic inclusion criteria with life expectancy exceeding 8 weeks. Paclitaxel was administered as a 3-hour infusion after premedication (dexamethasone, dexchlorpheniramine). Pharmacokinetic analysis and solvent assays (ethanol, cremophor) were performed during the first course. 20 courses were studied in 17 patients; 4 dosage levels were investigated (240 to 420 mg/m(2)). No dose-limiting haematological toxicity was observed. Severe acute neurological and allergic toxicity was encountered. One treatment-related death occurred just after the infusion at the highest dosage. Delayed peripheral neurotoxicity and moderate allergic reactions were also encountered. Pharmacokinetic analysis showed dose-dependent clearance of paclitaxel and elevated blood ethanol and **Cremophor EL** levels. Although no limiting haematological toxicity was reached, we do not recommend this paclitaxel schedule in children because of its acute neurological toxicity.

L132 ANSWER 4 OF 38 MEDLINE
ACCESSION NUMBER: 1998379918 MEDLINE
DOCUMENT NUMBER: 98379918 PubMed ID: 9716061
TITLE: Effects of Taxol on blood cells.
AUTHOR: Shimomura T; Fujiwara H; Ikawa S; Kigawa J; Terakawa N
SOURCE: LANCET, (1998 Aug 15) 352 (9127) 541-2.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917

Entered Medline: 19980908

L132 ANSWER 5 OF 38 MEDLINE
ACCESSION NUMBER: 1998338132 MEDLINE
DOCUMENT NUMBER: 98338132 PubMed ID: 9673415
TITLE: Cell line and schedule-dependent cytotoxicity of paclitaxel (Taxol): role of the solvent **Cremophor EL** /ethanol.
AUTHOR: Cordes N; Plasswilm L
CORPORATE SOURCE: Department of Radiation-Oncology, University Hospitals, Erlangen-Nuernberg, Germany.
SOURCE: ANTICANCER RESEARCH, (1998 May-Jun) 18 (3A) 1851-7. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980810

AB BACKGROUND: Paclitaxel's optimal dosage and scheduling is currently not determined. To compare paclitaxel (PTX) cytotoxicity in vitro, three cell lines were chosen for investigation by single versus fractionated exposure to Taxol and the diluent **Cremophor EL**/ethanol (CEL/eth). METHODS: An exponentially growing human lung-carcinoma (SK-LU-1), human glioblastoma (U-138 MG) and mammalian fibroblast cell line (HyB14FAF28) were used for colony forming assay examining cell survival, and flow cytometric DNA analysis by measuring cell cycle development. Tested concentrations varied from 2-50 microM and were incubated for 3 and 15 hours. Single (2-50 microM/d, especially 10 microM/d), versus fractionated (2 microM/d, day 1-5) exposure of Taxol and CEL/eth was investigated. As the control population, cells were exposed to a phosphate buffered solution (PBS). RESULTS: Control populations demonstrated an average survival of 90, 99 and 93% for SK-LU-1, U-138 MG, B14, respectively. Single Taxol exposure at 10 microM showed average survival of 54, 50 and 84% after 3 hours and 9, 48 and 82% after 15 hours for the above cell lines. Fractionated Taxol exposure with 2 microM/d, days 1-5 led to average survival of 55, 86 and 63%, respectively. Single CEL/eth exposure showed a cytotoxic effect with average survival of 94, 126 and 91% after 3 hours and 47, 63 and 88% after 15 hours respectively. Fractionated CEL/eth exposure showed an average survival of 67, 94 and 65% respectively. Flow cytometric analysis detected cell cycle shift concerning S- and G2/M-phase after Taxol exposure only in the two tumour cell lines, and not in the fibroblastic cells. CEL/eth was without significant effect on cell cycle distribution in all three cell lines. CONCLUSIONS: In the two human tumour cell lines cytotoxicity was more pronounced after prolonged Taxol exposure. The fibroblast cell line was not sensitive to single treatment, and was without cell cycle changes. Comparable to Taxol the diluent CEL/eth had a significant but less pronounced cytotoxic effect. Therefore, the cytotoxic mechanisms of paclitaxel's and CEL/eth's are worthy of further investigation.

L132 ANSWER 6 OF 38 MEDLINE
ACCESSION NUMBER: 1998124724 MEDLINE
DOCUMENT NUMBER: 98124724 PubMed ID: 9463563
TITLE: Cytotoxicity of fractionated paclitaxel (Taxol) administration in vitro.
AUTHOR: Plasswilm L; Cordes N; Fietkau R; Sauer R
CORPORATE SOURCE: Department of Radiooncology, University Erlangen-Nurnberg, Germany.
SOURCE: STRAHLENTHERAPIE UND ONKOLOGIE, (1998 Jan) 174 (1) 37-42. Journal code: 8603469. ISSN: 0179-7158.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980226

AB PURPOSE: Paclitaxel (Taxol) is a new anticancer agent with a novel mechanism of action. It has demonstrated broad clinical activity in a variety of malignancies. Several aspects of paclitaxel's usage remain to be clarified, including the optimal treatment schedule. Furthermore, the diluent of paclitaxel, **Cremophor EL**/ethanol, alone has shown to be markedly active in tumor samples. MATERIAL AND METHODS: The in-vitro cytotoxicity of paclitaxel (Taxol) due to single dose (1 x 10 microM/day, day 1 incubation time: 3 h and 15 h) and fractionated exposure (5 x 2 microM/day, day 1 to 5 incubation time: 3 h/day) was evaluated, measuring surviving fraction (clonogenic assay) and DNA distribution (flow cytometric analysis). In the control population, the diluent **Cremophor EL**/ethanol or a phosphate buffered salt solution (PBS) were applied using identical doses and schedules. A mammalian fibroblast cell line (HyB14FAF28) was used. RESULTS: Fractionated application of paclitaxel (Taxol) produced a significant lower clonogenic survival (0.63) in comparison with single dose exposure for 3 h (0.84) and 15 h (0.82). DNA analysis showed no evidence for a significant difference in DNA distribution of the paclitaxel-specific G2/M phase over a 10-day period. Controls with the diluent **Cremophor EL**/ethanol showed a clonogenic survival of 0.87 (3 h exposure) and 0.88 (15 h exposure) versus 0.65 after fractionated drug administration (5 x 2 microM/day, day 1 to 5, incubation time: 3 h/day). PBS controls and untreated controls did not show any significant effect. CONCLUSIONS: It seems that clonogenic survival after Taxol exposure of this mammalian fibroblast cell line varies with treatment schedule through a yet unknown process that does not involve G2/M arrest. The results indicate the treatment effects to be mainly based on the diluent combination without any further benefit induced by paclitaxel.

L132 ANSWER 7 OF 38 MEDLINE
ACCESSION NUMBER: 96176895 MEDLINE
DOCUMENT NUMBER: 96176895 PubMed ID: 8599876
TITLE: Plasma alcohol concentrations in patients following paclitaxel infusion.
AUTHOR: Webster L K; Crinis N A; Morton C G; Millward M J
CORPORATE SOURCE: Division of Research, Peter MacCallum Cancer Institute, Melbourne, Australia.
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (1996) 37 (5) 499-501.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960513
Last Updated on STN: 19980206
Entered Medline: 19960501

AB Paclitaxel is formulated in 50% **Cremophor El** and 50% ethanol such that patients receiving paclitaxel also receive a significant amount of each of these solvents. The aim of this study was to measure the plasma alcohol levels in patients treated with paclitaxel. A total of 12 patients who were enrolled in phase II trials of non-small-cell lung

cancer, breast cancer or ovarian cancer received 175 mg/m2 paclitaxel given as a 3-h infusion. Blood samples were obtained prior to and immediately following the infusion, and plasma ethanol concentrations were measured enzymatically. The dose of ethanol delivered with the paclitaxel ranged from 20.0 to 28.9 ml. No alcohol was detected in pre-dose plasma, but 8 of 12 patients had detectable levels in post-infusion plasma, with 0.033 g/dl being the highest concentration. The elimination rate of alcohol approximates the infusion rate when paclitaxel is given over 3h, resulting in low or undetectable levels in most patients. However, in patients receiving an equivalent dose of paclitaxel given as a 1-h infusion, the plasma alcohol levels will likely be high enough for significant pharmacological effects to occur.

L132 ANSWER 8 OF 38 MEDLINE
ACCESSION NUMBER: 97086521 MEDLINE
DOCUMENT NUMBER: 97086521 PubMed ID: 8932715
TITLE: Taxol from Pestalotiopsis microspora, an endophytic fungus of Taxus wallachiana.
AUTHOR: Strobel G; Yang X; Sears J; Kramer R; Sidhu R S; Hess W M
CORPORATE SOURCE: Department of Plant Pathology, Montana State University, Bozeman 59717, USA.
CONTRACT NUMBER: 1 ROI CA 58315-03 (NCI)
SOURCE: MICROBIOLOGY, (1996 Feb) 142 (Pt 2) 435-40.
Journal code: 9430468. ISSN: 1350-0872.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19990129
Entered Medline: 19961231

AB Pestalotiopsis microspora was isolated from the inner bark of a small limb of Himalayan yew, Taxus wallachiana, and was shown to produce taxol in mycelial culture. Taxol was identified by spectroscopic and chromatographic comparisons with authentic taxol. Optimal taxol production occurred after 2-3 weeks in still culture at 23 degrees C. [14C]Acetate and [14C]phenylalanine served as precursors for fungal [14C]taxol. These observations on P. microspora are discussed in relation to the biological importance of taxol production by fungi in general.

L132 ANSWER 9 OF 38 MEDLINE
ACCESSION NUMBER: 94361874 MEDLINE
DOCUMENT NUMBER: 94361874 PubMed ID: 7915908
TITLE: Paclitaxel-induced cytotoxicity--the effects of **cremophor EL** (castor oil) on two human breast cancer cell lines with acquired multidrug resistant phenotype and induced expression of the permeability glycoprotein.
COMMENT: Erratum in: Eur J Cancer 1994;30A(6):896
AUTHOR: Fjallskog M L; Frii L; Bergh J
CORPORATE SOURCE: Department of Oncology, University of Uppsala, Akademiska sjukhuset, Sweden.
SOURCE: EUROPEAN JOURNAL OF CANCER, (1994) 30A (5) 687-90.
Journal code: 9005373. ISSN: 0959-8049.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941021
Last Updated on STN: 19980206
Entered Medline: 19941013

AB Paclitaxel (Taxol) is a new cytotoxic agent with considerable activity in phase II studies on metastatic breast cancer. Paclitaxel for clinical use is dissolved in the solvents **cremophor EL** and ethanol.
In this study, we added paclitaxel, formulated either in **cremophor EL** and ethanol or only in ethanol, in increasing concentrations to two parental human breast cancer cell lines (ZR 75-1 and HS 578T) and their corresponding sublines with acquired doxorubicin resistance and P-glycoprotein expression. Paclitaxel dissolved either in ethanol or ethanol plus **cremophor EL**, resulted in steep and almost identical dose-response curves for the parental lines ZR 75-1 and HS 578T, respectively, independent of the solvent used. When paclitaxel was formulated only in ethanol the effects on the corresponding doxorubicin-resistant sublines were significantly reduced compared with paclitaxel dissolved in ethanol plus **cremophor EL**.
These effects by **cremophor EL** may partly explain some of the antitumoral effects observed by paclitaxel in anthracycline failing patients.

L132 ANSWER 10 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENTDUPLICATE 1
ACCESSION NUMBER: 2003-13594 DRUGU P G
TITLE: A lipophilic paclitaxel derivative incorporated in a lipid emulsion for parenteral administration.
AUTHOR: Lundberg B B; Risovic V; Ramaswamy M; Wasan K M
CORPORATE SOURCE: Univ.Abo; Univ.British-Columbia
LOCATION: Abo, Fin.; Vancouver, B.C., Can.
SOURCE: J.Controlled Release (86, No. 1, 93-100, 2003) 5 Fig. 22 Ref.
CODEN: JCREEC ISSN: 0168-3659
AVAIL. OF DOC.: Department of Biochemistry and Pharmacy, abo Akademi University, BioCity, P.O. Box 66, 20520 Abo, Finland. (e-mail: bolundbe@abo.fi).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The pharmacological prospects and the pharmacokinetic behavior of i.v. lipophilic paclitaxel (PA, Alexis) derivative, paclitaxel-oleate (PE), incorporated in a nano-size sterically **stabilized** oil-in-water lipid emulsion were studied in female rabbit (in vivo), and in human plasma and human cervical cancer cell line, HeLa (in vitro). Chemicals included in the preparation were egg phosphatidylcholine (lecithin), triolein, dipalmitoyl phosphatidyl ethanolamine, polyoxyethylenesorbitan monooleate (polysorbate-80), oleoyl chloride, carbonyldiimidazole (all Sigma-Chem.) and PEG-phosphatidylethanolamine. PE was cytotoxic against HeLa cells. I.v. 3H-PE in lipid emulsion had greater AUC, higher Cmax and lower systemic clearance than 3H-PA in **cremophor** -EL:ethylalcohol. It conclusion, sterically **stabilized** nano-size lipid emulsion can serve as drug-carrier for PE.

L132 ANSWER 11 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-33410 DRUGU G
TITLE: Manufacture and analysis of a paclitaxel concentrate for a solution for infusion in the hospital pharmacy.
AUTHOR: Theuer H; Scherbel G; Wilken A; Wendt J
LOCATION: Nuremberg; Waldbronn, Ger.
SOURCE: Krankenhauspharmazie (23, No. 3, 93-9, 2002) 8 Fig. 27 Ref.
CODEN: KRANDZ ISSN: 0173-7597
AVAIL. OF DOC.: Apotheke Klinikum Nuernberg Sued, Breslauer Strasse 201, 90471 Nuernberg, Germany. (e-mail: theuer@klinikum-nuernberg.de).
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB A paclitaxel (PX) infusion solution concentrate CS was manufactured using PX, **Cremophor** EL and anhydrous ethanol, and **stabilized** by deep-freezing it to temperatures below 20 deg. The long-term **stability** of this solution when **stored** in a frozen state protected from light was monitored over 12 wk and with only minor decomposition of the solution. The quality characteristics of the PX concentrate in terms of content and chromatographic purity corresponded to those of the proprietary medicinal product from the pharmaceutical industry. **Stabilization** of the solution by freezing thus appears an alternative to the **stabilization** methods described in the literature for PX concentrates, avoids patent infringement and enables hospital pharmacists to manufacture in-house a cheaper product of comparable quality to industrial preparations.

L132 ANSWER 12 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-46398 DRUGU P T S G
TITLE: Tumor targeting by conjugation of DHA to paclitaxel.
AUTHOR: Bradley M O; Swindell C S; Anthony F H; Witman P A; Devanesan P; Webb N L; Baker S D; Wolff A C; Donehower R C
CORPORATE SOURCE: Protarga; The-John-Hopkins-Oncol.Cent.
LOCATION: King of Prussia, Pa.; Baltimore, Md., USA
SOURCE: J.Controlled Release (74, No. 1-3, 233-36, 2001) 2 Fig. 9 Ref.
CODEN: JCREEC ISSN: 0168-3659
AVAIL. OF DOC.: Protarga Inc., 2200 Renaissance Blvd., Suite 450, King of Prussia, PA 19406, U.S.A. (e-mail: mbrad124@aol.com).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Tumor targeting, with concomitant long tumor exposure times, should increase the proportion of cells that move into cycle when the drug concentration is high, which should result in more tumor cell killing. To test this hypothesis, docosahexaenoic **acid** (DHA) was conjugated through an ester bond to the paclitaxel (PAC) 2'-oxygen. The resulting fatty **acid** conjugate (DHA-PAC) does not assemble microtubules and is non-toxic. The antitumor activity and pharmacokinetics of i.v. DHA-PAC were compared with those of free PAC (Taxol; Bristol-Squibb) in tumor-bearing mice. In addition, a phase I clinical study was conducted at The Johns Hopkins Hospital to evaluate the safety of DHA-PAC in patients with solid tumors. The primary side-effect was neutropenia. (conference paper: International Symposium on Tumor Targeted Delivery Systems, Bethesda, Maryland, USA, 2000).

L132 ANSWER 13 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1998-29318 DRUGU G
TITLE: Compatibility of paclitaxel in 5% glucose and 0.9% sodium chloride injections with EVA minibags.
AUTHOR: Xu Q A; Trissel L A; Davis M R
CORPORATE SOURCE: Univ.Texas-A+M-Syst.; Baxter-Healthcare
LOCATION: Houston, Tex., USA; Sydney, Austr.
SOURCE: Aust.J.Hosp.Pharm. (28, No. 3, 156-59, 1998) 2 Fig. 2 Tab. 5 Ref.
CODEN: AUHPAI ISSN: 0310-6810
AVAIL. OF DOC.: The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, U.S.A. (L.A.T.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Paclitaxel (PC, Anzatax, Faulding), formulated in **cremophor**-EL and ethyl-alcohol, was chemically **stable** at 0.3 and 1.2 mg/ml in 5% glucose injection and in 0.9% NaCl (both Am.Mcgaw) injection

solutions in ethylene-vinyl-acetate polymer (EVA, Baxter-Healthcare) minibags for up to 72 hr at 25 and 32 deg. Some material of unknown identity, but which was possibly polymer of varying associated acetate groups, was leached into the drug admixture from the container within 24 hr.

L132 ANSWER 14 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-13105 DRUGU P G S
TITLE: Liposomal delivery system for taxol.
AUTHOR: Shieh M F; Chu I M; Lee C J; Kan P; Hau D M; Shieh J J
CORPORATE SOURCE: Univ.Nat.Tsing-Hua
LOCATION: Hsinchu, Taiwan
SOURCE: J.Ferment.Bioeng. (83, No. 1, 87-90, 1997) 4 Fig. 2 Tab. 16 Ref.
CODEN: JFBIEX ISSN: 0922-338X
AVAIL. OF DOC.: Department of Chemical Engineering, National Tsing Hua University, Hsinchu, Taiwan 300, R.O.C.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Liposomal i.p. administration of taxol (Yunnan) was better than with ethanol:**Cremophor** EL, achieving greater **stability** and therapeutic effects in tumor-bearing mice, and fewer side-effects. A 7:3 ratio of egg phosphatidylcholine: dimyristoylphosphatidylglycerol (EPC:DMPG) with 40% cholesterol, 25% alpha-tocopherol (all Sigma-Chem.) and 3% taxol was the best formulation. **Storage** at 4 deg achieved the best **stability**. Mouse mortality and mean survival time were improved in the liposomal groups, and higher doses were tolerated. Mouse activity was greater in the liposomal group, compared to mice given the ethanol/**Cremophor** EL who were dazed and motionless.

L132 ANSWER 15 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-15739 DRUGU G
TITLE: The extraction of diethylhexylphthalate (DEHP) from polyvinyl chloride components of intravenous infusion containers and administration sets by paclitaxel injection.
AUTHOR: Allwood M C; Martin H
CORPORATE SOURCE: Univ.Derby
LOCATION: Derby, U.K.
SOURCE: Int.J.Pharm. (127, No. 1, 65-71, 1996) 2 Fig. 2 Tab. 12 Ref.
CODEN: IJPHDE ISSN: 0378-5173
AVAIL. OF DOC.: Medicines Research Unit, University of Derby, Mickleover, Derby DE3 5GX, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Paclitaxel (PT, Taxol) injection contains **cremophor** and ethanol, agents known to leach diethylhexylphthalate (DEHP) from PVC infusion bags and administration sets. The extent of DEHP extraction by PT injection contained in PVC i.v. infusion bags and given by either PVC or non-PVC sets was studied. During infusion, increasing amounts of DEHP were leached into the PT vehicle from PVC infusion bags and standard PVC sets. DEHP extracted was dependent on the concentration of the PT vehicle, the length of contact between injection vehicle and container and the type of administration set. DEHP level was at its lowest when a non-PVC set was used. The addition of PT to the infusate, administered by non-PVC sets, led to no increase in DEHP extraction. There is only minimal risk of DEHP exposure from PT infusion contained in PVC bags and given through non-PVC administration sets.

L132 ANSWER 16 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-19689 DRUGU G
TITLE: Parenteral formulations for the administration of paclitaxel.
AUTHOR: Simamora P; Dannenfelser R M; Tabibi S E; Yalkowsky S H
CORPORATE SOURCE: Univ.Arizona; Nat.Cancer-Inst.Bethesda
LOCATION: Tucson, Ariz.; Bethesda, Med., USA
SOURCE: Pharm.Res. (12, No. 9, Suppl., S-232, 1995)
CODEN: PHREEB ISSN: 0724-8741
AVAIL. OF DOC.: Department of Pharmaceutical Sciences, University of Arizona, Tucson, AZ 85721, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Paclitaxel is a natural product active against a number of human cancers. It is very insoluble in water and contains no groups that are ionizable in an acceptable pH range. It has a very low solubility in most cosolvents. The current FDA-approved paclitaxel formulation for i.v. administration contains an equal amount of **Cremophor** EL and ethanol. The former is notorious for producing allergic reactions. 2 Potential parenteral formulations containing 5 mg/ml and 3.5 mg/ml of taxol for i.v. administration that are **cremophor**-free and do not precipitate upon dilution have been developed. Both formulations were chemically and physically **stable** for at least 3 mth when **stored** at 4 deg. (conference abstract). (No EX).

L132 ANSWER 17 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1994-25127 DRUGU T P G
TITLE: Preparation, administration, **stability**, and compatibility with other medications.
AUTHOR: Goldspiel B R
LOCATION: Bethesda, Maryland, United States
SOURCE: Ann.Pharmacother. (28, No. 5, Suppl., S23-S26, 1994) 1 Fig. 1 Tab. 99 Ref.
CODEN: APHRER ISSN: 1060-0280
AVAIL. OF DOC.: Pharmacy Department, Warren G. Magnuson Clinical Center, Bethesda, MD 20892, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Preparation, administration, **stability** and compatibility of paclitaxel is reviewed. Taxol is the only available formulation and is formulated as a concentrated solution containing paclitaxel, **Cremophor** EL, polyoxyethylated **castor oil** and dehydrated alcohol. **Cremophor** EL leaches di(2-ethylhexyl) phthalate (dioctyl-phthalate, DEHP) from PVC i.v. tubings. DEHP is hepatotoxic and carcinogenic in animals. Preliminary studies suggest that triocytl trimellitrate (TOTM) leaches much less and is less hepatotoxic than DEHP. DEHP is not detected after **storage** in glass or polyolefin containers, but was present in large amounts after **storage** in PVC bags. The visual and turbidimetric compatibility of paclitaxel with other drugs is discussed.

L132 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
ACCESSION NUMBER: 2001:545477 CAPLUS
DOCUMENT NUMBER: 135:112075
TITLE: Purifying polyoxyethylated castor oils with activated charcoal and pharmaceutical formulations thereof
INVENTOR(S): Zhang, Kai; Smith, Gregory A.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052838	A1	20010726	WO 2001-US1749	20010119

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1251845	A1	20021030	EP 2001-904925	20010119

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: US 2000-177459P P 20000120
WO 2001-US1749 W 20010119

AB Disclosed are polyoxyethylated castor oils produced by prepg. a suspension of activated charcoal and a polyoxyethylated castor oil; and sepg. the activated charcoal from the polyoxyethylated castor oil. The process removes impurities such as colorants and alkali metal cations. Also disclosed are compns. contg. the treated castor oil and an active agent such as a pharmaceutical agent. The formulations have prolonged **storage stability**.

IT **64-17-5, Ethanol**, processes **77-92-9, Citric acid**, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(purifying polyoxyethylated castor oils with activated charcoal and pharmaceutical formulations)

IT **33069-62-4, Paclitaxel**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(purifying polyoxyethylated castor oils with activated charcoal and pharmaceutical formulations)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 1994:491880 CAPLUS
DOCUMENT NUMBER: 121:91880
TITLE: Injectable **taxol** composition
INVENTOR(S): Elliott, Robyn Louise; Handreck, Gregory Paul; Carver, David; Prout, Timothy; Ewald, Hernita
PATENT ASSIGNEE(S): F.H. Faulding and Co. Ltd., Australia
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9412198	A1	19940609	WO 1993-AU599	19931125

W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,

BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2149150	AA	19940609	CA 1993-2149150	19931118
CA 2308082	AA	19940609	CA 1993-2308082	19931118
EP 674510	A1	19951004	EP 1994-901593	19931118
EP 674510	B1	19980805		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

EP 835657	A1	19980415	EP 1997-121710	19931118

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE

AU 9351967	A1	19940609	AU 1993-51967	19931125
AU 667142	B2	19960307		
AU 9455538	A1	19940622	AU 1994-55538	19931125
ZA 9308844	A	19940802	ZA 1993-8844	19931126
CN 1096673	A	19941228	CN 1993-115293	19931126
CN 1095266	A	19941123	CN 1993-120529	19931127
CN 1047305	B	19991215		
US 6306894	B1	20011023	US 2000-563969	20000503
US 2003065022	A1	20030403	US 2001-970558	20011004

PRIORITY APPLN. INFO.:

AU 1992-6074	A	19921127
US 1992-995501	A	19921222
CA 1993-2149150	A3	19931118
EP 1994-901593	A3	19931118
WO 1993-US11209	W	19931118
WO 1993-AU599	W	19931125
US 1996-594478	A3	19960131
US 1997-979836	A1	19971126
US 1999-356158	A1	19990719
US 2000-563969	A1	20000503

AB An injectable soln. of taxol with improved stability has a pH less than 8.1, preferably 1 to 8, more preferably 5 to 7.5. The pH is adjusted by addn. of an acid, preferably citric acid, and the preferred compn. comprises taxol, Cremophor EL, citric acid and ethanol.

IT **33069-62-4, Taxol**
RL: BIOL (Biological study)
(injections contg. ethoxylated castor oil and citrate and, stable)

IT **64-19-7, Acetic acid**, biological studies
77-92-9, Citric acid, biological studies
RL: BIOL (Biological study)
(**taxol** injections contg. ethoxylated castor oils and)

IT **64-17-5, Ethanol**, biological studies
RL: BIOL (Biological study)
(**taxol** injections contg. ethoxylated castor oils and acid and)

L132 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:221488 CAPLUS
DOCUMENT NUMBER: 138:226787
TITLE: Injectable composition of **paclitaxel**
INVENTOR(S): Lee, Woo-Young; Lee, Sang-Heon; Kim, Kye-Hyun
PATENT ASSIGNEE(S): Choongwae Pharma Corporation, S. Korea
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022247	A1	20030320	WO 2002-KR1696	20020909

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: KR 2001-55511 A 20010910

AB The disclosure concerns an injectable compn. of paclitaxel, more particularly, an injectable compn. of paclitaxel having excellent anticancer effect comprising a solubilizer such as polyoxyl hydrogenated castor oil, anhyd. ethanol and stabilizer such as N-acetylamino acid. The injectable compns. of paclitaxel provide an effect higher than that of the known compns. showing not only a lower toxicity but also superior soly. of paclitaxel and stability at room temp., thus enabling venous injection by having fine particles. Paclitaxel (6 mg; 0.6%) was added to the soln. of 527 mg (56.7%) Cremophor EL and 0.5 mL anhyd. EtOH. The mixt. was stirred for 30 min to obtain the injectable compn. of Paclitaxel.

IT **64-17-5**, **Ethanol**, biological studies **77-92-9**, **Citric acid**, biological studies **33069-62-4**, **Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable compn. of **paclitaxel**)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:5758 CAPLUS
DOCUMENT NUMBER: 138:78450
TITLE: Particles with improved solubilization capacity
INVENTOR(S): Anderson, David M.
PATENT ASSIGNEE(S): Lyotropic Therapeutics, Inc, USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000236	A1	20030103	WO 2002-US19623	20020621

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003022242	A1	20030130	US 2002-176112	20020621

PRIORITY APPLN. INFO.: US 2001-300476P P 20010623

AB Structured materials and particles that are suitable for solubilizing poorly sol. and poorly-absorbed compds. at high loadings of active while minimizing the chance of pptn. of the active are described. A particle comprises a first vol. of hydrophobe-rich material with tunable dissoln. and solubilization characteristics and a distinct second vol. of nanostructural non-lamellar liq. cryst. material, the second vol. contg. the first domain and being capable of being in equil. with the first vol. Preferably, the nanostructured non-lamellar liq. cryst. material is capable of being in equil. with a polar solvent, a water-immiscible solvent or both. For example, 0.827 g of sweet basil oil was mixed with

0.765 g of the water-insol. surfactant Tween 85, 0.395 g of .alpha.-tocopherol, and 0.955 g water, and the mixt. was centrifuged for 16 h. At that time a basil oil-rich top phase had sepd. out which was decanted. A Tween-rich middle layer contg. a reversed-type liq. cryst. phase was present as well as a bottom aq. phase. About 4 mL of water was added to the middle and bottom layers and this mixt. sonicated forming a crude dispersion. Estradiol (15 mg) was dissolved in 0.594 g of the basil oil-rich top phase, and the following were overlaid on this soln.: 2.463 g of the crude dispersion, 2.452 g of water, 18 mg of sodium taurocholate and 28 mg of Pluronic F68. The mixt. was then sonicated, yielding microdroplets having an estradiol-contg. basil-rich core, coated by a reversed liq. cryst. material.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of particles with improved solubilization capacity contg. bioactive oil as liq. phase embedded within non-lamellar liq. crystals)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:923642 CAPLUS
DOCUMENT NUMBER: 136:74618
TITLE: Prodrug compounds with isoleucine
INVENTOR(S): Pickford, Lesley B.; Gangwar, Sanjeev; Lobl, Thomas J.; Nieder, Matthew H.; Yarranton, Geoffrey T.
PATENT ASSIGNEE(S): Corixa Corporation, USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001095943	A2	20011220	WO 2001-US18857	20010611
WO 2001095943	A3	20020829		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1294404	A2	20030326	EP 2001-944442	20010611

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: US 2000-211686P P 20000614
WO 2001-US18857 W 20010611

OTHER SOURCE(S): MARPAT 136:74618

AB The compds. of the invention are modified forms of therapeutic agents. A typical prodrug compd. of the invention comprises a therapeutic agent, an oligopeptide having an isoleucine residue, a stabilizing group and, optionally, a linker group. The prodrug is cleavable by an enzyme assocd. with the target cell. Methods of making and using the compds. are also disclosed.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug compds. with isoleucine)

IT **64-19-7, Acetic acid**, uses
RL: MOA (Modifier or additive use); USES (Uses)

(stabilizing agent; prodrug compds. with isoleucine)

L132 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730547 CAPLUS
DOCUMENT NUMBER: 135:293952
TITLE: Uses of metal salts to stabilize taxane-based compositions
INVENTOR(S): Zhang, Kai; Smith, Gregory A.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072300	A1	20011004	WO 2001-US9416	20010323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-191802P P 20000324

AB Disclosed are compns. contg. a taxane, a carrier and a metal salt of an acid. Also disclosed are methods of stabilizing taxane/carrier compns. and reducing degrdn. of taxanes, e.g., during storage. The methods entail including the metal salt in the taxane compn. or pretreating the carrier with the metal salt, optionally in combination with other pretreatments. The presence of Zn, Fe, or Cu gluconates and FeSO4 decreased degrdn. of paclitaxel in formulations pretreated with Cremophor EL.

IT **77-92-9, Citric acid**, biological studies
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metal salts to stabilize taxane-based compns.)

IT **33069-62-4, Paclitaxel**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metal salts to stabilize taxane-based compns.)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730546 CAPLUS
DOCUMENT NUMBER: 135:278040
TITLE: Taxane-based compositions
INVENTOR(S): Zhang, Kai; Smith, Gregory A.; Gutierrez-Roca, Jose C.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072299	A1	20011004	WO 2001-US9382	20010323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-191802P P 20000324

AB Taxane-based compns. and methods of using the same to achieve target blood levels of a taxane in a mammal, e.g., to treat taxane-responsive malignant and non-malignant diseases, are described. Compns. comprise a taxane, a carrier, a co-solubilizer, and a stabilizer in a form suitable for oral administration to a mammal and they exhibit long-term stability and overall palatability. Methods for using taxane-based compns. as anal. tools for pharmacokinetic studies are also disclosed. For example, a soln. was prepd. contg. Paclitaxel 12 mg, vitamin E TPGS 400.00 mg, propylene glycol 400.00 mg, ascorbyl palmitate 5.0 mg, dl-.alpha.-tocopherol 5.0 mg and d Dehydrated alc. to 1.0 mL.

IT **33069-62-4, Paclitaxel**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(bioavailability, palatability, and stability of oral taxane-based compns.)

IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, esters
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bioavailability, palatability, and stability of oral taxane-based compns.)

IT **105454-04-4**, 7-Epitaxol
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(degrdn. product; bioavailability, palatability, and stability of oral taxane-based compns.)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:228688 CAPLUS
DOCUMENT NUMBER: 134:271250
TITLE: Surface modified particulate pharmaceutical compositions containing surfactants
INVENTOR(S): Pace, Gary W.; Mishra, Awadhesh K.; Snow, Robert A.
PATENT ASSIGNEE(S): RTP Pharma Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021154	A2	20010329	WO 2000-US25880	20000921
WO 2001021154	A3	20011025		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1214059 A2 20020619 EP 2000-970467 20000921
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
JP 2003509453 T2 20030311 JP 2001-524580 20000921
PRIORITY APPLN. INFO.: US 1999-154964P P 19990921
WO 2000-US25880 W 20000921

AB This invention disclosure relates to compns. for the delivery of stable surface modified sub-micron and micron sized particles of water-insol. drugs from a non-aq. medium that self-disperses on exposure to an aq. environment. Thus, compns. of cyclosporine that self-disperse into surface-modified micron- or sub-micron-sized particle suspensions contained cyclosporine 50, Epax 451O-TG 150, vitamin E-TPGS 45, Tween 80 405, and EtOH 150 mg.

IT **64-19-7**, **Acetic acid**, biological studies
77-92-9, **Citric acid**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aq. medium contg.; surface modified particulate pharmaceutical compns. contg. surfactants)

IT **64-17-5**, **Ethanol**, biological studies **33069-62-4**
, **Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surface modified particulate pharmaceutical compns. contg. surfactants)

L132 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:31306 CAPLUS
DOCUMENT NUMBER: 134:105846
TITLE: Clear aqueous dispersions of triglycerides and surfactants for delivery of drugs and nutrients
INVENTOR(S): Chen, Feng-Jing; Patel, Mahesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001001960	A1	20010111	WO 2000-US15133	20000602
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6267985	B1	20010731	US 1999-345615	19990630
EP 1194120	A1	20020410	EP 2000-938039	20000602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003503440	T2	20030128	JP 2001-507455	20000602

PRIORITY APPLN. INFO.: US 1999-345615 A 19990630
WO 2000-US15133 W 20000602

AB The present invention relates to drug and nutrient delivery systems, and in particular to pharmaceutical compns. and methods for improved solubilization of triglycerides and improved delivery of therapeutic agents. Compns. of the present invention include a triglyceride and a

carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the triglyceride and surfactants. An optional therapeutic agent can be incorporated into the compn., or can be co-administered with the compn. The invention also provides methods of enhancing triglyceride soly. and methods of treatment with therapeutic agents using these compns. Several formulations were presented of compns. that can be prepd. according to the present invention using a variety of therapeutic agents. Examples of aq. dispersions include: (1) Cremophor RH-40 0.75, Peceol 0.25, corn oil 0.40, and fenofibrate 0.10; (2) Cremophor RH-40 0.57, Crovol M-40 0.43, corn oil 0.40, and Rofecoxib 0.15; (3) Tween 80 0.70, Tween 85 0.35, Miglyol 812 0.30, Paclitaxel 0.10, and PEG 400 0.25; or (4) Kessco PEG 400 MO 0.33, corn oil 0.30, and Terbinafine 0.25 parts, resp.

IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, esters **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clear aq. dispersions of triglyceride and surfactants for delivery of drugs and nutrients)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:911036 CAPLUS
DOCUMENT NUMBER: 134:76383
TITLE: Oral pharmaceutical compositions containing taxanes
INVENTOR(S): Gutierrez-Rocca, Jose C.; Cacace, Janice L.; Selim, Sami; Testman, Robert; Rutledge, J. Michael
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078247	A1	20001228	WO 1999-US13821	19990618
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9946955	A1	20010109	AU 1999-46955	19990618
BR 9917403	A	20020709	BR 1999-17403	19990618
EP 1221908	A1	20020717	EP 1999-930408	19990618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
JP 2003502349	T2	20030121	JP 2001-504316	19990618

PRIORITY APPLN. INFO.: WO 1999-US13821 A 19990618

AB Pharmaceutical compns. for oral administration to mammalian subjects comprise a taxane or taxane deriv. (e.g., paclitaxel or docetaxel) as active ingredient and a vehicle comprising at least 30% by wt. of a carrier for the taxane, the carrier having an HLB value of at least about 10. The compns. may also comprise 0-70% of a viscosity-reducing co-solubilizer. The compns. may be incorporated into conventional oral pharmaceutical dosage forms, or can be in the form of a 2-part drug

wherein the first part includes the taxane in a solubilizing vehicle and the second part comprises a carrier for the taxane to promote oral absorption. Methods of treatment of taxane-responsive disease conditions employing the novel compns. are also disclosed, whereby the compns. can be administered alone or in assocn. with an oral bioavailability enhancing agent. A formulation contg. Tween 80 at 18 mg/kg and paclitaxel gave an abs. bioavailability of 54% which was >15% for i.v. drug.

IT **33069-62-4, Paclitaxel**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(oral pharmaceuticals contg. taxanes)

IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, esters
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceuticals contg. taxanes)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:608551 CAPLUS
DOCUMENT NUMBER: 133:213151
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6294192	B1	20010925	US 1999-258654	19990226
NZ 513810	A	20010928	NZ 2000-513810	20000105
EP 1158959	A1	20011205	EP 2000-901394	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537317	T2	20021105	JP 2000-600619	20000105
US 2002012680	A1	20020131	US 2001-898553	20010702
US 6451339	B2	20020917		

PRIORITY APPLN. INFO.: US 1999-258654 A 19990226
WO 2000-US165 W 20000105

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the surfactants contg. the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical compn. contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium

taurocholate 0.26, and propylene glycol 0.46 mg.
IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, diglycerides **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:378166 CAPLUS
DOCUMENT NUMBER: 133:22425
TITLE: Stabilized injectable pharmaceutical compositions containing taxoid antineoplastic agents
INVENTOR(S): Owens, Walter H.; Irby, Timothy
PATENT ASSIGNEE(S): Mylan Pharmaceuticals, Inc., USA
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6071952	A	20000606	US 1998-203350	19981202
US 6153644	A	20001128	US 1999-432084	19991102
WO 2000032186	A2	20000608	WO 1999-US28268	19991201
WO 2000032186	A3	20001116		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1135120	A2	20010926	EP 1999-964007	19991201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-203350 A3 19981202
WO 1999-US28268 W 19991201

AB The long term **storage stability** of injectable pharmaceutical compns. comprising a taxane or taxoid is improved by incorporating an effective amt. of an antioxidant. In an injectable container, 1.8 g of paclitaxel were mixed with 150 mL of dehydrated alc., 150 mL of polyethylene glycol 400, and 50.0 mL of an aq. 0.05% thiophenol soln. and stirred vigorously to assure complete soln. To the soln. was added sodium metabisulfite and Cremophor EL-P to make 0.01% and 50% in the soln. The soln. was stored for 5 h ate 105.degree.. Antioxidant stabilized formulation yielded an impurity profile with a lower overall total impurities content as compared with the controls.
IT **33069-62-4, Paclitaxel**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized injectable pharmaceutical compns. contg. taxoid antineoplastic agents)
IT **105454-04-4**, 7-epi-**Taxol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized injectable pharmaceutical compns. contg. taxoid antineoplastic agents)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:640689 CAPLUS
DOCUMENT NUMBER: 131:262644
TITLE: Anticancer **storage stable** self-emulsifying preconcentrate compositions
INVENTOR(S): Parikh, Indu; Moussa, Iskandar; Carrier, Alain
PATENT ASSIGNEE(S): Rtp Pharma Inc., USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9949848	A1	19991007	WO 1999-US7162	19990330
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326485	AA	19991007	CA 1999-2326485	19990330
AU 9933770	A1	19991018	AU 1999-33770	19990330
EP 1067908	A1	20010117	EP 1999-915190	19990330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002509877	T2	20020402	JP 2000-540814	19990330
SE 2000003449	A	20001123	SE 2000-3449	20000927

PRIORITY APPLN. INFO.:
US 1998-80272P P 19980401
US 1998-80273P P 19980401
WO 1999-US7162 W 19990330

AB Pharmaceutical dosage forms for anticancer drugs, and paclitaxel in particular, are described in which the active drug is formulated as **storage stable** self-emulsifying preconc. A compn. contained Miglyol 840 1.971, Cremophor RH40 2.190, Imwitor 308 0.767, Labrasol 0.548, and paclitaxel 0.175 g.

IT **64-17-5, Ethanol**, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer **storage stable** self-emulsifying preconc. compns.)

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer **storage stable** self-emulsifying preconc. compns.)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:220012 CAPLUS
DOCUMENT NUMBER: 130:242336
TITLE: Pharmaceuticals in parenteral formulations containing plasma protein
INVENTOR(S): Hegedus, Lajos; Krempels, Krisztina; Paal, Krisztina; Petho, Gabor

Searched by Barb O'Bryen, STIC 308-4291

PATENT ASSIGNEE(S): Human Rt., Hung.
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913914	A1	19990325	WO 1998-HU86	19980917
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893623	A1	19990405	AU 1998-93623	19980917
AU 734695	B2	20010621		
EP 981375	A1	20000301	EP 1998-946629	19980917
EP 981375	B1	20030108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001508806	T2	20010703	JP 1999-517576	19980917
NZ 503302	A	20010831	NZ 1998-503302	19980917
BR 9812469	A	20020205	BR 1998-12469	19980917
AT 230611	E	20030115	AT 1998-946629	19980917
ZA 9808585	A	20000313	ZA 1998-8585	19980918
LV 12493	B	20010120	LV 2000-38	20000314
NO 2000001371	A	20000518	NO 2000-1371	20000316
LT 4736	B	20001227	LT 2000-18	20000317

PRIORITY APPLN. INFO.: HU 1997-1554 A 19970918
WO 1998-HU86 W 19980917

OTHER SOURCE(S): MARPAT 130:242336

AB The invention is related to water-sol. products and pharmaceutical formulations in solid or liq. form mainly for parenteral use. They consist of or comprise a therapeutically active substance (having low aq. soly. and a substantial binding affinity to plasma proteins) and a plasma protein fraction in controlled aggregation state, whereby the said active substance and the said protein fraction are bound to each other by way of noncovalent bonds. It also covers processes for the prepn. of the product and pharmaceutical formulation.

IT **64-17-5**, **Ethanol**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(pharmaceuticals in parenteral compns. contg. plasma protein)

IT **33069-62-4**, **Paclitaxel**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceuticals in parenteral compns. contg. plasma protein)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:655956 CAPLUS
DOCUMENT NUMBER: 131:291282
TITLE: Nonaqueous compositions for parenteral administration comprising a saccharide fatty acid ester
INVENTOR(S): Johnson, David Farley; Quinlan, James M.
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5965603	A	19991012	US 1998-111951	19980708
BR 9802492	A	20000118	BR 1998-2492	19980720

PRIORITY APPLN. INFO.: US 1997-53234P P 19970721
CA 1997-2211949 A 19970729

AB Nonaq. compns. comprising a saccharide fatty acid ester and an active compd. is provided. The nonaq. compns. of this invention may be parenterally administered to animals and humans. In particular, the nonaq. compns. of the present invention are useful for preventing, controlling or treating helminth, acarid or arthropod endo- or ectoparasitic infection or infestation in warm-blooded animals. A non aq. compn. contained moxidectin 1.05, sucrose monolaurate 10.00, ethanol 20.00, and propylene glycol 67.85%. The compn. remained as a **stable** clear soln. after 18 mo **storage** at 30.degree.. Serum level of moxidectin in cattles treated with the compn. was studied.

IT **33069-62-4, Paclitaxel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonaq. compns. for parenteral administration comprising saccharide fatty acid ester)

IT **64-17-5, Ethanol**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(nonaq. compns. for parenteral administration comprising saccharide fatty acid ester)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:589441 CAPLUS
DOCUMENT NUMBER: 131:276889
TITLE: Pharmacopeia versus practice: extraction of di(2-ethylhexyl) phthalate from PVC by the solvents of **paclitaxel**, docetaxel, and etoposide
AUTHOR(S): Kalmeijer, M. D.; Lauwen, J.; Stuurman, A.
CORPORATE SOURCE: Neth.
SOURCE: Pharmaceutisch Weekblad (1999), 134(33), 1143-1149
CODEN: PHWEAW; ISSN: 0031-6911
PUBLISHER: Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie
DOCUMENT TYPE: Journal
LANGUAGE: Dutch

AB Extn. of di(2-ethylhexyl) phthalate (DEHP) from PVC by the solvents of paclitaxel, docetaxel, and etoposide was studied. These solvents were: (a) for paclitaxel: abs. alc. 39.6 g, Cremophor EL to 100 mL; (b) for docetaxel: abs. alc. 13.0, distd. H2O 87.0 g; to 75 mL of this mixt. was added 25 mL polysorbate 80; (c) for etoposide: citric acid monohydrate 209, PhCH2OH 3.0, polysorbate 80 8.0, PEG-300 65.0 g, and abs. alc. to 100 mL. Two methods of extn. were compared: (1) extn. according to the procedure used in the European Pharmacopeia to test PVC containers for blood and blood components for DEHP release (1 h at 37.degree.); (2) extn. at room temp. during the period the prepd. soln. is allowed to be kept according to the product information. The 3 solvents were tested by both methods in 3 different concns. corresponding to body surfaces of 1.5, 2, and 2.5 m2. All samples were analyzed by HPLC. The use of paclitaxel and etoposide solvents resulted in a .apprx.6-fold higher concns. of DEHP with method 2 than with method 1. For the docetaxel solvent, the DEHP concns. found with both methods were comparable. Evidently the method of the

European Pharmacopeia is not suitable for predicting DEHP extn. in practice. The extd. quantities of DEHP with method 2 were .apprx.3.5-fold higher with the etoposide solvent than with the docetaxel solvent. Both still complied with European Pharmacopeia requirements, though administration of docetaxel in PVC is not allowed in the United States. With the paclitaxel solvent, DEHP release exceeded twice the Pharmacopeia limit.

IT **33069-62-4, Paclitaxel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(infusion; pharmacopeia vs. practice: extn. of di(ethylhexyl) phthalate from PVC by solvents of **paclitaxel**, docetaxel, and etoposide)

IT **77-92-9**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent contg.; pharmacopeia vs. practice: extn. of di(ethylhexyl) phthalate from PVC by solvents of **paclitaxel**, docetaxel, and etoposide)

IT **64-17-5, Ethanol**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent; pharmacopeia vs. practice: extn. of di(ethylhexyl) phthalate from PVC by solvents of **paclitaxel**, docetaxel, and etoposide)

L132 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:503255 CAPLUS
DOCUMENT NUMBER: 127:113384
TITLE: Pharmaceutical injection containing taxane with improved solubility and toxicity properties
INVENTOR(S): Almassian, Bijan; Choy, William
PATENT ASSIGNEE(S): Genelabs Technologies, Inc., USA; Almassian, Bijan; Choy, William
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9723208	A1	19970703	WO 1996-US20187	19961219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2240595	AA	19970703	CA 1996-2240595	19961219
AU 9712949	A1	19970717	AU 1997-12949	19961219
AU 724842	B2	20000928		
EP 876145	A1	19981111	EP 1996-943805	19961219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1209059	A	19990224	CN 1996-199939	19961219

PRIORITY APPLN. INFO.: US 1995-576204 A2 19951221
WO 1996-US20187 W 19961219

AB The title injection is claimed. The injection soln. comprises a taxane, such as taxol or docataxel, in a pharmaceutically pure form, a polyoxyethylene sorbitan fatty acid monoester, polyethoxylated castor oil, and ethanol. The polysorbitan and polyethoxylated castor oil are present in amts. effective to reduce the toxicity of the taxane relative to the

toxicity obsd. when either the polysorbitan or polyethoxylated castor oil is used in the absence of the other. An injection soln. contained PEG-300 20, ethanol 10, Cremophor EL 15, Tween 80 5 mL, taxol (I) 300, and anhyd. citric acid 100 mg. The amt. of I in the soln. after 12 wk storage at 37.degree. was 98.7%.

IT **64-17-5, Ethanol.**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(pharmaceutical injection contg. taxane with improved soly. and toxicity properties)

IT **77-92-9, Citric acid**, biological studies
33069-62-4, Taxol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical injection contg. taxane with improved soly. and toxicity properties)

L132 ANSWER 35 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002446622 EMBASE
TITLE: Dosing sequence-dependent pharmacokinetic interaction of oxaliplatin with paclitaxel in the rat.
AUTHOR: Liu J.; Kraut E.H.; Balcerzak S.; Grever M.; D'Ambrosio S.; Chan K.K.
CORPORATE SOURCE: K.K. Chan, College of Pharmacy, Ohio State University, Columbus, OH 43210, United States. chan.56@osu.edu
SOURCE: Cancer Chemotherapy and Pharmacology, (2002) 50/6 (445-453).
Refs: 26
ISSN: 0344-5704 CODEN: CCPHDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: In a phase I clinical trial of oxaliplatin (OPT) in combination with paclitaxel (PXL), a pharmacokinetic interaction was observed when OPT was given as a 2-h i.v. infusion followed by a 1-h i.v. infusion of PXL. The purpose of this study was to use a rat model to evaluate whether the pharmacokinetic interaction between OPT and PXL is dosing sequence-dependent. Methods: One group of rats was given OPT as a 2-h i.v. infusion followed by a 1-h i.v. infusion of PXL formulated in 50% Cremophor EL (CrEL)/50% ethanol (OPT.fwdarw.fPXL), similar to the current phase I clinical protocol. In a second group of rats, the fPXL was infused first to reach a quasi-steady-state plasma level of PXL, followed by an i.v. bolus dose of OPT (CIfPXL.fwdarw.OPT). In a third group of rats, fPXL was replaced with the formulation vehicle, CrEL, which was infused in the same manner as in the second group. Each combination was accompanied with a control of either OPT alone or with replacement of PXL with dextrose 5% in water (CID5W.fwdarw.OPT). The total platinum (Pt) levels in plasma and plasma ultrafiltrate were measured by a validated inductively coupled plasma mass spectrometry (ICPMS) method. The protein binding, red blood cell (RBC) uptake and urinary elimination of Pt were also examined in each group of rats. Results: The concentration-time profiles of plasma Pt and ultrafiltrable Pt followed triexponential decays in all groups of rats. In the rat receiving OPT.fwdarw.fPXL, the terminal elimination rate constant (.gamma.) of plasma Pt increased, with essentially no change in the total body clearance (CL) and the AUC value, when compared to those without PXL infusion (CID5W.fwdarw.OPT). The (steady-state volume of distribution (V(ss)) of the ultrafiltrable Pt also showed an increase in the combination group receiving OPT.fwdarw.fPXL ($P < 0.01$). These results were similar to those from the clinical trial, although the magnitude of change was less. However, in the CIfPXL.fwdarw.OPT group, both CL and V(ss) of Pt in plasma and plasma ultrafiltrate decreased, with corresponding increases

in AUCs ($P < 0.01$). The 24-h urinary elimination of total Pt increased in both combination groups, irrespective of the dosing sequence. No difference in protein binding of Pt was observed among the groups. There was a decrease in RBC uptake in the presence of steady-state level of fPXL, but the same was not observed in the OPT.fwdarw.fPXL group. Additionally, similar results were observed with OPT in combination with CrEL alone. Conclusions: These results suggest that alterations in the pharmacokinetics of OPT by fPXL are dosing sequence-dependent and mainly caused by the formulation vehicle CrEL. It is suggested that the dosing sequence of fPXL followed by OPT would be more clinically favorable because it would prolong the residence of OPT in systemic circulation. It is further recommended that the use of other formulations of PXL without CrEL or docetaxel would avoid the complication effect of CrEL.

L132 ANSWER 36 OF 38 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-062579 [08] WPIDS
DOC. NO. CPI: C2001-017625
TITLE: Kit for preparing stable **paclitaxel** formulation for use as anticancer agent, comprising separately stored drug, solution of anhydrous **citric acid** in **ethanol** and solution of polyethoxylated **castor oil** in **ethanol**.
DERWENT CLASS: B02
INVENTOR(S): ORTNER, P
PATENT ASSIGNEE(S): (PBSP-N) PBS PHARM BULK SUBSTANCES SA
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19925211	A1	20001207	(200108)*		3

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19925211	A1	DE 1999-19925211	19990601

PRIORITY APPLN. INFO: DE 1999-19925211 19990601
AB DE 19925211 A UPAB: 20010207
NOVELTY - A kit for preparing a stable **paclitaxel** (I) formulation comprises three sealed sterile vials, respectively containing:
(i) a defined amount of (I);
(ii) a defined solution (A) of anhydrous **citric acid** in **ethanol**; and
(iii) a defined solution (B) of **Cremophor** EL (RTM; polyethoxylated **castor oil**) or **Cremophor** ELP (RTM; polyethoxylated **castor oil**) in **ethanol**

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(a) a method for preparing a (I) formulation, by dissolving a specific amount of (I) in a specific amount of solution (A), adding a specific amount of solution (B) and shaking the mixture until homogeneous; and
(b) the formulation obtained by method (a).
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - (I) is a cytostatic/cytotoxic agent, useful for treating cancer, e.g. ovarian cancer, breast cancer, lung cancer or leukemia.
ADVANTAGE - Separate storage of the drug, solvent and stabilizer components avoids the stability problems of prior art solution formulations of (I), is less expensive and allows long-term storage.

Concentrated formulations obtained using the kit are chemically, pharmaceutically and microbiologically stable for at least one year. Ready-for-use preparations can be produced rapidly and easily, e.g. by diluting the concentrated formulations with a conventional infusion solution.
Dwg.0/0

L132 ANSWER 37 OF 38 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-571683 [48] WPIDS
DOC. NO. CPI: C1999-166772
TITLE: Taxane composition used for treating e.g. cancer and malaria .
DERWENT CLASS: A23 A25 A96 B02 B04
INVENTOR(S): MCCHESNEY-HARRIS, L L
PATENT ASSIGNEE(S): (NAPR-N) NAPRO BIO THERAPEUTICS INC; (MCCH-I) MCCHESNEY-HARRIS L L
COUNTRY COUNT: 77
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9945918	A1	19990916	(199948)*	EN	45
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AL AU BA BB BG BR CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA UZ VN YU					
ZA 9901885	A	19991027	(199951)		42
AU 9929022	A	19990927	(200006)		
EP 977562	A1	20000209	(200012)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
BR 9904856	A	20000718	(200042)		
CN 1255852	A	20000607	(200046)		
MX 9910340	A1	20000401	(200124)		
KR 2001012363	A	20010215	(200154)		
US 2001029264	A1	20011011	(200162)		
JP 2001524988	W	20011204	(200203)		46

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9945918	A1		WO 1999-US5151	19990310
ZA 9901885	A		ZA 1999-1885	19990309
AU 9929022	A		AU 1999-29022	19990310
EP 977562	A1		EP 1999-909941	19990310
			WO 1999-US5151	19990310
BR 9904856	A		BR 1999-4856	19990310
			WO 1999-US5151	19990310
CN 1255852	A		CN 1999-800022	19990310
MX 9910340	A1		MX 1999-10340	19991110
KR 2001012363	A		KR 1999-710315	19991108
US 2001029264	A1	Provisional	US 1998-77459P	19980310
		Cont of	US 1999-265649	19990310
			US 2001-795626	20010228
JP 2001524988	W		JP 1999-546025	19990310
			WO 1999-US5151	19990310

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9929022	A	Based on	WO 9945918

EP 977562 A1 Based on WO 9945918
BR 9904856 A Based on WO 9945918
JP 2001524988 W Based on WO 9945918

PRIORITY APPLN. INFO: US 1998-77459P 19980310; US 1999-265649 19990310; US 2001-795626 20010228

AB WO 9945918 A UPAB: 19991122
NOVELTY - Composition comprises a taxane and at least one of d- alpha -tocopheryl polyethylene glycol succinate (TPGS), dimethylisosorbide, **citric acid**, methoxy PEG 350, PEG 300 and PEG 4600.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - Used for treating ovarian, prostate or breast cancers, malignant lymphoma, lung cancer, melanoma, Kaposi's sarcoma, polycystic kidney disease, Alzheimer's disease, malaria and rheumatoid arthritis.
ADVANTAGE - The composition has improved stability compared with previous formulations of **paclitaxel**, overcoming its water insolubility and prevents allergic reactions or other side effects. The composition has longer shelf life.
Dwg.0/0

L132 ANSWER 38 OF 38 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-417987 [35] WPIDS
DOC. NO. CPI: C1999-122731
TITLE: Stabilized **paclitaxel** formulations contain e.g. **citric acid**, **ethanol**, a polyglycol ester of 12-hydroxystearic acid and PEG, and an organic solvent e.g. triacetin.
DERWENT CLASS: A28 A96 B02
INVENTOR(S): BURCHETT, M K; CODDINGTON, C A; RAGHAVAN, R; SPEICHER, E R
PATENT ASSIGNEE(S): (ABBO) ABBOTT LAB
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5922754	A	19990713	(199935)*		5
WO 2000020036	A1	20000413	(200026)	EN	
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9958225	A	20000426	(200036)		
EP 1117440	A1	20010725	(200143)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2002526424	W	20020820	(200258)		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5922754	A	US 1998-165930	19981002
WO 2000020036	A1	WO 1999-US21024	19990914
AU 9958225	A	AU 1999-58225	19990914
EP 1117440	A1	EP 1999-945661	19990914
		WO 1999-US21024	19990914
JP 2002526424	W	WO 1999-US21024	19990914
		JP 2000-573394	19990914

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9958225	A	Based on	WO 200020036

EP 1117440 A1 Based on WO 200020036
JP 2002526424 W Based on WO 200020036

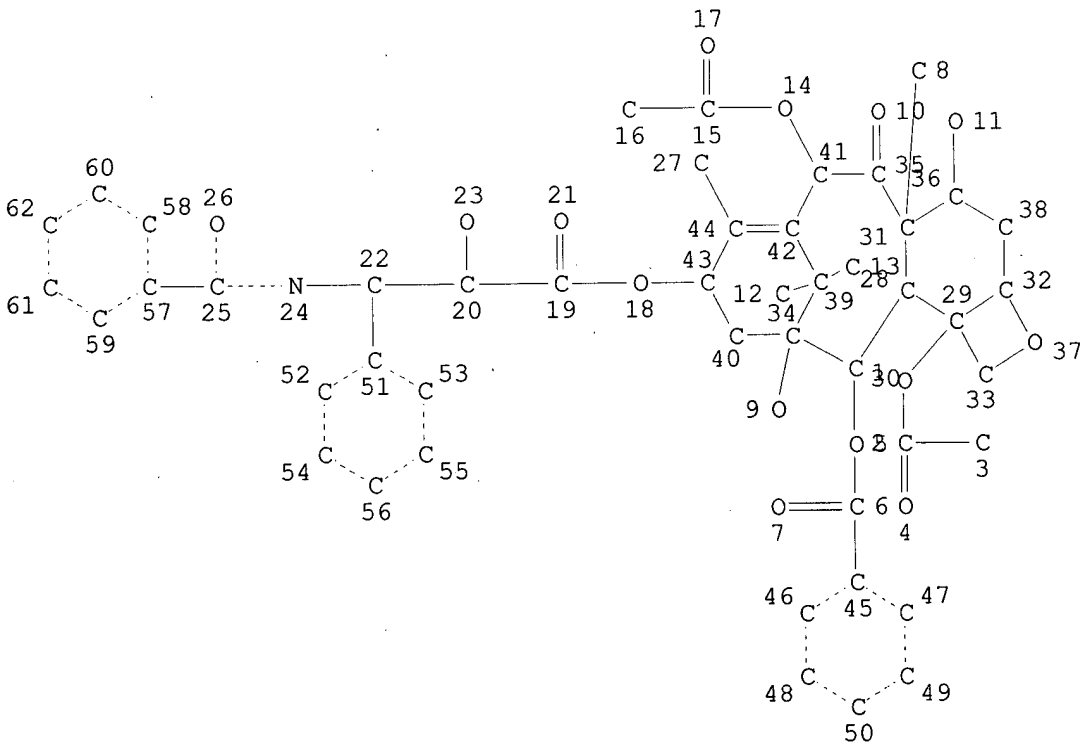
PRIORITY APPLN. INFO: US 1998-165930 19981002
AB US 5922754 A UPAB: 19990902
NOVELTY - A composition comprising **paclitaxel**, acid, water, alcohol, a polyglycol ester of 12-hydroxystearic acid and polyethylene glycol, and one or more organic solvents, is new.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - For providing **paclitaxel** formulations which may be terminally sterilized and which show long term stability in water containing mixtures.
ADVANTAGE - **Paclitaxel** compositions can be stabilized without use of **Cremophor** EL(RTM) which has been implicated in causing anaphylactic reactions in some patients. The compositions have extended stability compared to prior art compositions.
Dwg.0/0

=> fil capl; d que l47
FILE 'CAPLUS' ENTERED AT 12:40:55 ON 10 APR 2003

FILE COVERS 1907 - 10 Apr 2003 VOL 138 ISS 15
FILE LAST UPDATED: 9 Apr 2003 (20030409/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L6 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 62

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STEREO ATTRIBUTES: NONE
L8            71 SEA FILE=REGISTRY FAM FUL L6
L13         7488 SEA FILE=CAPLUS ABB=ON  (PACLITAXEL OR TAXOL)/OBI
L14         6976 SEA FILE=CAPLUS ABB=ON  L8
L35       163717 SEA FILE=CAPLUS ABB=ON  SEAL?
L37      2855053 SEA FILE=CAPLUS ABB=ON  ACID#/OBI
L39       417775 SEA FILE=CAPLUS ABB=ON  STOR?
L43       502709 SEA FILE=CAPLUS ABB=ON  CONTAINER# OR VIAL# OR BOTTLE# OR
                 TUBE#
L45       635612 SEA FILE=CAPLUS ABB=ON  CLOS####
L47            5 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND (L35 OR L45 OR L39)
                 AND L37 AND L43

=> s l47 not l130
L133           5 L47 NOT L130

=> fil medl; d que 168; d que 169

FILE 'MEDLINE' ENTERED AT 12:40:57 ON 10 APR 2003

  FILE LAST UPDATED: 9 APR 2003 (20030409/UP).  FILE COVERS 1958 TO DATE.

  On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

  MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
  MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/summ2003.html
  for a description on changes.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L57         3004 SEA FILE=MEDLINE ABB=ON  DRUG PACKAGING/CT
L68            6 SEA FILE=MEDLINE ABB=ON  L50 AND L57


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L55         3038 SEA FILE=MEDLINE ABB=ON  DRUG STORAGE/CT
L56        24342 SEA FILE=MEDLINE ABB=ON  DRUG STABILITY/CT
L69            3 SEA FILE=MEDLINE ABB=ON  L50 AND L56 AND L55

=> s (l68-169) not l131
L134           9 ((L68 OR L69)) NOT L131

=> fil embase; d que 186; d que 187; d que 189

FILE 'EMBASE' ENTERED AT 12:40:58 ON 10 APR 2003
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  FILE COVERS 1974 TO 3 Apr 2003 (20030403/ED)

  EMBASE has been reloaded. Enter HELP RLOAD for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.
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previously printed

previously printed

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L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L79         1218 SEA FILE=EMBASE ABB=ON  DRUG PACKAGING/CT
L86            2 SEA FILE=EMBASE ABB=ON  L70 AND L79


L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L77         2954 SEA FILE=EMBASE ABB=ON  DRUG STORAGE/CT
L87            3 SEA FILE=EMBASE ABB=ON  L70 AND L77


L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L71        76078 SEA FILE=EMBASE ABB=ON  ALCOHOL/CT
L72         6717 SEA FILE=EMBASE ABB=ON  CITRIC ACID/CT
L73        11020 SEA FILE=EMBASE ABB=ON  ACETIC ACID/CT
L74          137 SEA FILE=EMBASE ABB=ON  RICINOMACROGOL/CT
L75          893 SEA FILE=EMBASE ABB=ON  CASTOR OIL/CT
L76          728 SEA FILE=EMBASE ABB=ON  CREMOPHOR/CT
L78        19703 SEA FILE=EMBASE ABB=ON  DRUG STABILITY+NT/CT
L82        81481 SEA FILE=EMBASE ABB=ON  "CARBOXYLIC ACIDS AND THEIR DERIVATIVES
              "+NT/CT
L89            4 SEA FILE=EMBASE ABB=ON  L70 AND L78 AND ((L71 OR L72 OR L73 OR
              L74 OR L75 OR L76) OR L82)


=> s (l86 or l87 or l89) not l85
L135           8 (L86 OR L87 OR L89) NOT L85

=> fil drugu; d que l109

FILE 'DRUGU' ENTERED AT 12:41:00 ON 10 APR 2003
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FILE LAST UPDATED: 8 APR 2003       <20030408/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L100         802 SEA FILE=DRUGU ABB=ON  PACKAG?
L101         686 SEA FILE=DRUGU ABB=ON  SHELF LIFE
L102         819 SEA FILE=DRUGU ABB=ON  SEAL###
L109           3 SEA FILE=DRUGU ABB=ON  L90 AND (L100 OR L101 OR L102)


=> s l109 not l112
L136           3 L109 NOT L112

=> fil wpids; d que l129; s l129 not l120

FILE 'WPIDS' ENTERED AT 12:41:02 ON 10 APR 2003
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FILE LAST UPDATED:          7 APR 2003      <20030407/UP>
MOST RECENT DERWENT UPDATE:     200323        <200323/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L113        1452 SEA FILE=WPIDS ABB=ON  PACLITAXEL OR TAXOL
L115      813664 SEA FILE=WPIDS ABB=ON  ACID#
L121      906950 SEA FILE=WPIDS ABB=ON  CONTAINER# OR VIAL# OR BOTTLE# OR TUBE#

L122     1137573 SEA FILE=WPIDS ABB=ON  SEAL? OR CLOS####
L123      168528 SEA FILE=WPIDS ABB=ON  PACKAG?
L129           7 SEA FILE=WPIDS ABB=ON  L113 AND L115 AND (L121 OR L123) AND
                 L122

L137           6 L129 NOT L120   previously printed

=> dup rem l134,l136,l133,l135,l137
FILE 'MEDLINE' ENTERED AT 12:41:44 ON 10 APR 2003

FILE 'DRUGU' ENTERED AT 12:41:44 ON 10 APR 2003
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PROCESSING COMPLETED FOR L134
PROCESSING COMPLETED FOR L136
PROCESSING COMPLETED FOR L133
PROCESSING COMPLETED FOR L135
PROCESSING COMPLETED FOR L137
L138          31 DUP REM L134 L136 L133 L135 L137 (0 DUPLICATES REMOVED)
                 ANSWERS '1-9' FROM FILE MEDLINE
                 ANSWERS '10-12' FROM FILE DRUGU
                 ANSWERS '13-17' FROM FILE CAPLUS
                 ANSWERS '18-25' FROM FILE EMBASE
                 ANSWERS '26-31' FROM FILE WPIDS

=> d ibib ab hitrn 1-31; fil hom

L138 ANSWER 1 OF 31     MEDLINE
ACCESSION NUMBER:   1999394835     MEDLINE
```

DOCUMENT NUMBER: 99394835 PubMed ID: 10466923
TITLE: Paclitaxel compatibility with ethylene vinyl acetate bags.
AUTHOR: Goldspiel B R
SOURCE: ANNALS OF PHARMACOTHERAPY, (1999 Jul-Aug) 33 (7-8) 873-4.
Journal code: 9203131. ISSN: 1060-0280.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014

L138 ANSWER 2 OF 31 MEDLINE
ACCESSION NUMBER: 1999356591 MEDLINE
DOCUMENT NUMBER: 99356591 PubMed ID: 10427584
TITLE: Physico-chemical stability of docetaxel premix solution and docetaxel infusion solutions in PVC bags and polyolefine containers.
AUTHOR: Thiesen J; Kramer I
CORPORATE SOURCE: Department of Pharmacy, J. Gutenberg University Hospital, Germany.
SOURCE: PHARMACY WORLD AND SCIENCE, (1999 Jun) 21 (3) 137-41.
Journal code: 9307352. ISSN: 0928-1231.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990920

AB We assessed the physical and chemical stability of docetaxel infusion solutions. Stability of the antineoplastic drug was determined 1.) after reconstitution of the injection concentrate and 2.) after further dilution in two commonly used vehicle-solutions, 0.9% sodium chloride and 5% dextrose, in PVC bags and polyolefine containers. Chemical stability was measured by using a stability-indicating HPLC assay with ultraviolet detection. Physical stability was determined by visual inspection. The stability tests revealed that reconstituted docetaxel solutions (= premix solutions) are physico-chemically stable (at a level > or = 95% docetaxel) for a minimum of four weeks, independent of the storage temperature (refrigerated, room temperature). Diluted infusion solutions (docetaxel concentration 0.3 mg/ml and 0.9 mg/ml), with either vehicle-solution, proved physico-chemically stable (at a level > or = 95% docetaxel) for a minimum of four weeks, when prepared in polyolefine containers and stored at room temperature. However, diluted infusion solutions exhibited limited physical stability in PVC bags, because docetaxel precipitation occurred irregularly, though not before day 5 of storage. In addition, time-dependent DEHP-teaching from PVC infusion bags by docetaxel infusion solutions must be considered.

L138 ANSWER 3 OF 31 MEDLINE
ACCESSION NUMBER: 1999222341 MEDLINE
DOCUMENT NUMBER: 99222341 PubMed ID: 10205627
TITLE: Compatibility of paclitaxel in 5% glucose solution with ECOFLAC low-density polyethylene containers-stability under different storage conditions.
AUTHOR: Sautou-Miranda V; Brigas F; Vanheerswynghels S; Chopineau J
CORPORATE SOURCE: Laboratoire de Pharmacie Clinique et Biotechnique, UFR Pharmacie, Clermont-FD, France.
SOURCE: INTERNATIONAL JOURNAL OF PHARMACEUTICS, (1999 Feb 1) 178

(1) 77-82.
Journal code: 7804127. ISSN: 0378-5173.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990518

AB The compatibility of paclitaxel with low-density polyethylene containers (ECOFLAC) was studied under different temperature and light conditions. Solutions of 0.4 and 1.2 mg/ml of paclitaxel in 5% glucose solution were prepared, put into ECOFLAC containers and stored: (i) at ambient temperature (20-25 degrees C) and in ambient light; (ii) at ambient temperature in the dark; and (iii) at +4 degrees C in the dark. Paclitaxel was assayed by high-performance liquid chromatography after visual inspection of the solutions. The results show that solutions of TAXOL in 5% glucose should not be stored for more than 5 days in glass or ECOFLAC containers because a whitish precipitate tends to form, lowering the paclitaxel concentration. The decrease in the paclitaxel concentration observed after chromatographic analysis ranged very widely (from 12 to 83% of the initial concentration). However solutions of TAXOL diluted in 5% glucose was stable for 5 days in ECOFLAC containers under all the storage conditions tested. These additive-free low-density polyethylene containers offer the advantage of not releasing DEHP into the paclitaxel solutions.

L138 ANSWER 4 OF 31 MEDLINE
ACCESSION NUMBER: 96323928 MEDLINE
DOCUMENT NUMBER: 96323928 PubMed ID: 8739262
TITLE: Plasticizer extraction of Taxol infusion solution from various infusion devices.
AUTHOR: Mass B; Huber C; Kramer I
CORPORATE SOURCE: Apotheke, Klinikum J. Gutenberg Universitat, Mainz, Germany.
SOURCE: PHARMACY WORLD AND SCIENCE, (1996 Apr) 18 (2) 78-82.
Journal code: 9307352. ISSN: 0928-1231.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961022
Last Updated on STN: 19961022
Entered Medline: 19961010

AB Taxol solution extracts the plasticizer DEHP (di(2-ethylhexyl)phthalate) from polyvinyl chloride (PVC) materials. In order to minimize patient exposure to DEHP, Taxol solutions should be prepared and administered in PVC-free materials. Particulate matter may form in Taxol infusion solution over time, so that in-line filtration with microporous membranes not greater than 0.22 microns is advisable. The purpose of this study was to evaluate the suitability of various administration- and in-line filter-sets for Taxol application. The extent of leached DEHP was determined using a Reversed Phase HPLC assay specific for DEHP. The four tested administration-sets, labeled as PVC-free, were all found to be suitable for Taxol application. The tested standard PVC-lined administration-set should not be used for Taxol application. Baxter Intermate LV 250 can be recommended as a disposable infusion device for ambulatory Taxol application. It can be connected with all the tested filter sets.

L138 ANSWER 5 OF 31 MEDLINE
ACCESSION NUMBER: 95160005 MEDLINE

DOCUMENT NUMBER: 95160005 PubMed ID: 7856630
TITLE: Paclitaxel diluent and the case of the slippery spike.
AUTHOR: Martin M; Bepko R
SOURCE: AMERICAN JOURNAL OF HOSPITAL PHARMACY, (1994 Dec 15) 51 (24) 3078, 3080.
Journal code: 0370474. ISSN: 0002-9289.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950316

L138 ANSWER 6 OF 31 MEDLINE
ACCESSION NUMBER: 95023594 MEDLINE
DOCUMENT NUMBER: 95023594 PubMed ID: 7937531
TITLE: Novel taxol formulations: preparation and characterization of taxol-containing liposomes.
AUTHOR: Sharma A; Straubinger R M
CORPORATE SOURCE: Department of Pharmaceutics, University at Buffalo, State University of New York, Amherst 14260-1200.
CONTRACT NUMBER: CA55251 (NCI)
SOURCE: PHARMACEUTICAL RESEARCH, (1994 Jun) 11 (6) 889-96.
Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19980206
Entered Medline: 19941109

AB Taxol is a promising anticancer agent under investigation for therapy of ovarian, breast, colon, and head and neck cancer. One problem associated with the administration of taxol is its low solubility in most pharmaceutically-acceptable solvents; the formulation used clinically contains Cremophor.EL (polyethoxylated castor oil) and ethanol as excipients, which cause serious adverse effects. To eliminate this vehicle and possibly improve the antitumor efficacy of taxol, we have formulated taxol in liposomes of various compositions. Liposome formulations containing taxol and phospholipid in the molar ratio 1:33 were prepared from phosphatidylglycerol (PG) and phosphatidylcholine (PC) (1:9 molar ratio), and were physically and chemically stable for more than 2 months at 4 degrees C, or for 1 month at 20 degrees C. A method of producing taxol-liposomes by lyophilization has been developed, by which large batches can be prepared reproducibly in a 'pharmaceutically rational' manner. Taxol-liposomes retained the growth-inhibitory activity of the free drug in vitro against a variety of tumor cell lines. In mice, taxol-liposomes were well-tolerated when given in bolus doses by both iv and ip routes. The Maximum Tolerated Dose (MTD) was > 200 mg/kg; it exceeded that of free taxol, which had a MTD of 30 mg/kg by iv or 50 mg/kg by ip administration. Free taxol administered in the Cremophor vehicle was toxic at doses > 30 mg/kg, as was the equivalent volume of vehicle without drug.(ABSTRACT TRUNCATED AT 250 WORDS)

L138 ANSWER 7 OF 31 MEDLINE
ACCESSION NUMBER: 94218300 MEDLINE
DOCUMENT NUMBER: 94218300 PubMed ID: 7909371
TITLE: A mixed micellar formulation suitable for the parenteral administration of taxol.
AUTHOR: Alkan-Onyuksel H; Ramakrishnan S; Chai H B; Pezzuto J M

CORPORATE SOURCE: Department of Pharmaceutics and Pharmacodynamics, College of Pharmacy, University of Illinois at Chicago 60612.
CONTRACT NUMBER: 2-507-RR 05893-07 (NCRR)
SOURCE: PHARMACEUTICAL RESEARCH, (1994 Feb) 11 (2) 206-12. Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940606
Last Updated on STN: 19970203
Entered Medline: 19940524

AB Taxol is a promising antitumor agent with poor water solubility. Intravenous administration of a current taxol formulation in a non-aqueous vehicle containing Cremophor EL may cause allergic reactions and precipitation upon aqueous dilution. In this study a novel approach to formulate taxol in aqueous medium for i.v. delivery is described. The drug is solubilized in bile salt (BS)/phospholipid (PC) mixed micelles. The solubilization potential of the mixed micelles increased as the total lipid concentration and the molar ratio of PC/BS increased. Precipitation of the drug upon dilution was avoided by the spontaneous formation of drug-loaded liposomes from mixed micelles. The formulation can be stored in a freeze-dried form as mixed micelles to achieve optimum stability, and liposomes can be prepared by simple dilution just before administration. As judged by a panel of cultured cell lines, the cytotoxic activity of taxol was retained when formulated as a mixed-micellar solution. Further, for the same solubilization potential, the mixed-micellar vehicle appeared to be less toxic than the standard nonaqueous vehicle of taxol containing Cremophor EL.

L138 ANSWER 8 OF 31 MEDLINE
ACCESSION NUMBER: 94169491 MEDLINE
DOCUMENT NUMBER: 94169491 PubMed ID: 7907239
TITLE: Paclitaxel stability and compatibility in polyolefin containers.
AUTHOR: Chin A; Ramakrishnan R R; Yoshimura N N; Jeong E W; Nii L J; DiMeglio L S
CORPORATE SOURCE: School of Pharmacy, University of Southern California (USC).
SOURCE: ANNALS OF PHARMACOTHERAPY, (1994 Jan) 28 (1) 35-6. Journal code: 9203131. ISSN: 1060-0280.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19950206
Entered Medline: 19940413

AB OBJECTIVE: To determine the compatibility and stability of paclitaxel in polyolefin containers. DESIGN: The following paclitaxel concentrations were determined by a stability-indicating HPLC method: 0.3 and 1.2 mg/mL diluted in dextrose 5% for injection, USP (D5W) or sodium chloride 0.9% for injection, USP (NS). The solutions were prepared in polyolefin containers and the stability and compatibility were monitored for 48 hours when stored at ambient temperature (20-23 degrees C) and normal fluorescent lighting. A mixture of the drug carrier consisting of approximately 10% polyoxyethylated castor oil (Cremophor EL) and 10% ethanol in D5W and NS, without paclitaxel, was studied to differentiate the effect of paclitaxel from the effect of the drug carrier on the container. Paclitaxel concentrations, pH changes, and visual clarity were used as stability and compatibility indicators. RESULTS: Paclitaxel

concentrations remained at 96-99 percent of the initial concentration for up to 48 hours when placed in the polyolefin containers. No changes in color or visual clarity were noted. Only minor changes in the pH of the admixtures were observed. CONCLUSIONS: Paclitaxel diluted in D5W or NS at concentrations of 0.3 and 1.2 mg/mL is stable and compatible in flexible, polyolefin containers for up to 48 hours.

L138 ANSWER 9 OF 31 MEDLINE
ACCESSION NUMBER: 91353631 MEDLINE
DOCUMENT NUMBER: 91353631 PubMed ID: 1679294
TITLE: Stability, compatibility, and plasticizer extraction of taxol (NSC-125973) injection diluted in infusion solutions and stored in various containers.
AUTHOR: Waugh W N; Trissel L A; Stella V J
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kansas, Lawrence 66045.
CONTRACT NUMBER: NO1-CM-67912 (NCI)
NO1-CM-97576 (NCI)
SOURCE: AMERICAN JOURNAL OF HOSPITAL PHARMACY, (1991 Jul) 48 (7) 1520-4.
Journal code: 0370474. ISSN: 0002-9289.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911020
Last Updated on STN: 19950206
Entered Medline: 19911001

AB The stability of taxol (NSC-125973) in various diluents and containers was determined, and the extent of leaching of di(2-ethylhexyl) phthalate (DEHP) from polyvinyl chloride (PVC) bags caused by the taxol formulation was measured. A taxol formulation consisting of a 6-mg/mL solution of taxol in 50% polyoxyethylated castor oil and 50% dehydrated ethanol was added to 50- and 100-mL glass bottles, PVC infusion bags, and polyolefin containers containing 5% dextrose injection or 0.9% sodium chloride injection to give initial nominal taxol concentrations of 0.3, 0.6, 0.9, and 1.2 mg/mL. The containers were maintained at 20-23 degrees C for 12-24 hours. Samples were assayed by stability-indicating high-performance liquid chromatography, and clarity was determined visually. An experiment was run to ascertain whether DEHP would leach from a PVC administration set during a simulated infusion. There was no substantial loss of taxol over 24 hours. Filtration through a membrane resulted in no loss of taxol. All the solutions initially appeared hazy. Solutions stored in PVC bags became more hazy with time than solutions stored in glass or polyolefin containers. The haze seen in PVC bags was traced to leaching of DEHP. Agitation had no effect on the extent of leaching. Leaching was also seen during simulated delivery through PVC administration sets. No DEHP was detected when solutions were stored in glass or polyolefin containers and infused through polyethylene-lined sets. At the dilutions studied, taxol was visually and chemically stable for up to 24 hours.(ABSTRACT TRUNCATED AT 250 WORDS)

L138 ANSWER 10 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-26328 DRUGU P
TITLE: Nocodazole treatment of CV-1 cells enhances nuclear/perinuclear accumulation of lipid-DNA complexes and increases gene expression.
AUTHOR: Lindberg J; Fernandez M A M; Dezz Ropp J; Hamm Alvarez S F
CORPORATE SOURCE: Univ.Southern-California; Valentis
LOCATION: Los Angeles, Burlingame; Alviso, Cal., USA
SOURCE: Pharm.Res. (18, No. 2, 246-49, 2001) 3 Fig. 1 Tab. 8 Ref.
CODEN: PHREEB ISSN: 0724-8741

AVAIL. OF DOC.: USC School of Pharmacy, 1985 Zonal Avenue, Los Angeles, California 90089-9121, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Nocodazole enhanced the nuclear/perinuclear targeting of lipid-DNA complexes in parallel with increased gene expression of the transfected DNA in CV-1 cells. Nocodazole induced a slight loss of microtubule (MT) polymer during pre-treatment, while taxol increased MT polymer content and accumulation of MT bundles. Nocodazole increased the expression of the luciferase gene encased in either 1-(2-(9-(Z)-octadecenoyloxy))-2-(8)(Z)-heptadecenyl)-3-(hydroxyethyl)imidazolinium chloride (DOTIM):Diphytanoyl phosphoethanolamine (PE) and DOTIM:1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), while taxol had no detectable effect. Results suggest that it is conceivable that the effects of nocodazole on gene targeting and persistence may occur through a MT-independent mechanism.

L138 ANSWER 11 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-36784 DRUGU T S
TITLE: A phase I study of hycamtin following paclitaxel and carboplatin in first line therapy for ovarian cancer.
AUTHOR: Sadozye A; Chan S; Carmichael J
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Obstet.Gynaecol. (106, No. 9, 998-99, 1999)
CODEN: BJOGAS ISSN: 0306-5456
AVAIL. OF DOC.: Queen Elisabeth Hospital, Gateshead, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The standard regimen of paclitaxel 175 mg/sq.m plus carboplatin AUC 6 every 3 wk for 5 cycles followed by 5 cycles of hycamtin (topotecan) 1.25-1.5 mg/sq.m every 3 wk were studied in 30 patients in an open label phase I study. The maximum tolerated dose was reached at 1.5 mg/sq.m for hycamtin. Myelosuppression was the main dose limiting toxicity. In the 1.25 mg/sq.m group 50% of patients had grade III and 16% had grade IV hematological toxicity. In the 1.5 mg/sq.m, 10% patients had grade III and 90% patients had grade IV hematological toxicity. It was concluded that a phase III study should be carried out with the 3 drugs in the above sequence with the dose of hycamtin at 1.25 mg/sq.m (day 1-5). (conference abstract: Spring Scientific Meeting of the British Gynaecological Cancer Society, Liverpool, U.K., 1999). (No EX).

L138 ANSWER 12 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-43391 DRUGU G
TITLE: Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization.
AUTHOR: Loftsson T; Brewster M E
CORPORATE SOURCE: Univ.Iceland
LOCATION: Reykjavik, Iceland
SOURCE: J.Pharm.Sci. (85, No. 10, 1017-25, 1996) 2 Fig. 7 Tab. 108 Ref.
CODEN: JPMSAE ISSN: 0022-3549
AVAIL. OF DOC.: Department of Pharmacy, University of Iceland, P.O. Box 7210, IS-127 Reykjavik, Iceland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Pharmaceutical applications of cyclodextrins (CD) are reviewed. The molecular structure of these glucose derivatives, which approximates a

truncated cone or torus, generates a hydrophilic exterior surface and a nonpolar cavity. CD can interact with appropriately sized molecules leading to the formation of inclusion complexes. These noncovalent complexes offer a variety of physicochemical advantages over the free drugs including enhanced aqueous solubility and solution stability. Chemical modification of the parent CD can lead to enhanced drug complexation and interaction. The stabilizing/destabilizing effects of CD on chemically labile drugs are evaluated.

L138 ANSWER 13 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:564887 CAPLUS
DOCUMENT NUMBER: 135:142255
TITLE: Drug delivery systems for treatment of restenosis and anastomotic intimal hyperplasia
INVENTOR(S): Helmus, Michael N.; Cunanan, Crystal; Tremble, Patrice
PATENT ASSIGNEE(S): Edwards Lifesciences Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001054748	A1	20010802	WO 2001-US2563	20010125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1250166	A1	20021023	EP 2001-905081	20010125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-178087P P 20000125
WO 2001-US2563 W 20010125

AB The invention provides methods for treating injuries to 1 or more internal structures of a subject by administering a drug delivery vehicle to an external surface of the injured structure. The drug delivery vehicle substantially adheres to the site of administration and provides for the release of a bioactive agent that reduces or prevents further injury to the internal structure by disease processes, such as hyperplasia. Thus, a fibrin polymer formulation, polymd. from a mixt. contg. a final concn. of 25-30 mg/mL fibrinogen, 5 IU human factor XIII, 50 IU human thrombin, and paclitaxel was prepd. Also, each **vial** of paclitaxel formulated in delayed-release microspheres was reconstituted with 4 mL sterile saline, and 2 mL of this mixt. was added per **vial** of a **Sealant** Protein Conc. Anal. of the data obtained by angiog. suggested there was no significant difference between control, vehicle and paclitaxel treatment groups.

IT **33069-62-4, Paclitaxel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug delivery systems for treatment of restenosis and anastomotic intimal hyperplasia)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L138 ANSWER 14 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:265217 CAPLUS
DOCUMENT NUMBER: 134:285587
TITLE: Improved methods for delivering bioactive agents using vesicles and ultrasound energy
INVENTOR(S): Unger, Evan C.
PATENT ASSIGNEE(S): ImaRx Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001024705	A1	20010412	WO 2000-US27025	20000929
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001051131	A1	20011213	US 1999-413110	19991006

PRIORITY APPLN. INFO.: US 1999-413110 A 19991006
US 1996-666129 A3 19960619
US 1999-290324 A2 19990412

AB Methods for enhancing the bioavailability of a bioactive agent in vivo are disclosed. Embodiments of the invention involve administering a bioactive agent and an acoustically active compn. to a patient. Ultrasound energy may be applied in an amt. sufficient to activate the acoustically active compn. In preferred form, the acoustically active compn. is administered to the patient at a rate which comprises continuous infusion. To a soln. of saline, propylene glycol, and glycerol (8:1:1) were added dipalmitoyopyosphatidylcholine, dipalmitoylphyosphatidylethanolamine-polyethylene glycol-5000, and dipalmitoylphosphatidic acid in a molar ratio of 82:8:10. The resulting mixt. was heated to about 45.degree. and filtered. The filtered mixt. was placed in a **vial** and allowed to cool to room temp. The **vial** was placed under vacuum to evacuate any gas, after which the **vial** was pressurized with perfluoropropane gas. The **vial** was then **sealed,** placed on a shaker and agitated at room temp. to provide a soln. of perfluoropropane-filled vesicles having a mean diam. of about 2.5 .mu.m. The concn. of vesicles in the soln. was about 1.5x109 vesicle/mL.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improved methods for delivering bioactive agents using vesicles and ultrasound energy)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L138 ANSWER 15 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:906093 CAPLUS
DOCUMENT NUMBER: 136:25134
TITLE: Use of ultrasound for delivering bioactive agents
INVENTOR(S): Unger, Evan C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 38 pp., Cont.-in-part of U. S. Ser. No. 290,324.
CODEN: USXXCO

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001051131	A1	20011213	US 1999-413110	19991006
US 6033645	A	20000307	US 1996-666129	19960619
WO 2001024705	A1	20010412	WO 2000-US27025	20000929

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1996-666129 A3 19960619
US 1999-290324 A2 19990412
US 1999-413110 A 19991006

AB Methods for enhancing the bioavailability of a bioactive agent in vivo is disclosed. Embodiments of the invention involve administering a bioactive agent and an acoustically active compn. to a patient. Ultrasound energy may be applied in an amt. sufficient to activate the acoustically active compn. In preferred form, the acoustically active compn. is administered to the patient at a rate which comprises continuous infusion. To a soln. of saline, propylene glycol and glycerol (8:1:1) were added dipalmitoylphosphatidyl-choline,dipalmitoylphosphatidylethanolamine-PEG5000 and dipalmitolylphosphatidic acid in a molar ratio of 82:8:10. The resulting mixt. was heated to about 45.degree., filtered, and cooled to room temp. The **vial** contg. the mixt. was placed under vacuum to evacuate any gas, after which the **vial** was pressurized with perfluoropropane (PFP). The **vial** was then **sealed**, placed on a shaker and agitated at room temp. to provide a soln. of PFP-filled vesicles having a mean diam. of about 2.5 mm. The soln. of PFP-vesicles was administered i.v. to a healthy human subject at a dose of about 10 mL per Kg of body wt., providing a vesicle dose of about 1.5x107 vesicles/Kg. After injection, a saline flush (5 mL) was administered in the same injection site. Transducers (2.5, 3.5 and 5.0 MHz) were used to image the heart region in both short-axis and long-axis views. After injection of the saline flush, the ultrasound image rapidly darkened until the heart was not visible due to severe shadowing. This severe shadowing lasted for a period of time of about 30 s to about 1 min. Upon dissipation of the shadowing, the ultrasound image revealed only transient contrast enhancement of the myocardial tissues.

IT **33069-62-4, Paclitaxel**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of ultrasound for delivering bioactive agents)

L138 ANSWER 16 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:401630 CAPLUS
DOCUMENT NUMBER: 133:34450
TITLE: Pharmaceutical compositions based on phospholipids and polymers
INVENTOR(S): Leigh, Steven; Leigh, Mathew Louis Steven
PATENT ASSIGNEE(S): Phares Pharmaceutical Research N.V., Neth. Antilles
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000033817	A1	20000615	WO 1999-GB4070	19991208
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
GB 2344520	A1	20000614	GB 1998-27006	19981208
EP 1137402	A1	20011004	EP 1999-961183	19991208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002532389	T2	20021002	JP 2000-586310	19991208

PRIORITY APPLN. INFO.:
GB 1998-27006 A 19981208
GB 1999-25365 A 19991027
WO 1999-GB4070 W 19991208

AB The present invention relates to the prepn. of powder or solid compns. comprising single and double chain amphiphilic lipids in assocn. with polymers which harden them so that they can be comminuted into powder or granules. The compns. can act as carriers for biol. active compds. and can be administered to living organisms. Such a compn. may comprise a biol. active compd. and monoacyl and diacyl membrane lipid in assocn. with a polymer, said compn. being a solid that when **stored** in a glass **container** remains free flowing after 3 mo at 40 >C and 75 % relative humidity. The lipids may be selected from those which have GRAS (generally regarded as safe) status, e.g. enzyme-modified lecithin, and the polymer may be selected from natural polysaccharide polymers, starches and their derivs., cellulose and its derivs. and gelatins. For example, a solid formulation was prepd. contg. flurbiprofen, VP 200 (a lipid contg. 60% by wt. of monoacyl phosphatidylcholine and 40% phosphatidylcholine), and Eudragit in a ratio of 1:10:10, resp. The compn. may be filled into hard gelatin capsules or may be compressed into tablets.

IT **33069-62-4, Taxol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. based on phospholipids and polymers)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L138 ANSWER 17 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:865092 CAPLUS
DOCUMENT NUMBER: 134:21486
TITLE: Kit for the production of a formulation of **paclitaxel**
INVENTOR(S): Ortner, Peter
PATENT ASSIGNEE(S): PBS Pharmaceutical Bulk Substances S.A., Switz.
SOURCE: Ger. Offen., 4 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19925211	A1	20001207	DE 1999-19925211	19990601

PRIORITY APPLN. INFO.:
DE 1999-19925211 19990601

AB A kit for the prodn. of a pharmaceutical formulation of paclitaxel, in which the individual components in kept sep. sterile **closed containers**. The formulation is chem. and microbiol. stable. Thus, paclitaxel was mixed with a soln. of citric acid in EtOH (soln. A) and kept in a **vial**. A soln. B consisting of Cremophor EL or Cremophor ELP in EtOH was added to the soln. A. The mixt. was stirred to homogeneity and the conc. obtained can be used for the prepn. of an infusion soln.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kit for prodn. of formulation of **paclitaxel**)

L138 ANSWER 18 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003092701 EMBASE
TITLE: Optimising the therapeutic trinity of active ingredient, delivery system and functional packaging.
AUTHOR: Sam T.
CORPORATE SOURCE: T. Sam, NV Organon, P.O. Box 20, 5340 BH Oss, Netherlands. tom.sam@organon.com
SOURCE: Journal of Controlled Release, (21 Feb 2003) 87/1-3 (153-157).
Refs: 6
ISSN: 0168-3659 CODEN: JCREEC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This paper introduces the "therapeutic trinity" concept for formulating and developing optimal drug products. It starts with the recognition that all drug products are constituted of three distinct elements: the active ingredient, the delivery system and the packaging. Union of these three elements into one trinity will bring therapeutic value to the patient under the condition that active ingredient, delivery system and packaging are developed and optimised interdependently. Optimisation should be performed with the patient in mind, taking into account the relevant efficacy and safety parameters, and the relevant quality and cost parameters. Since the patient plays the central role in the performance of the drug product, biopharmaceutical robustness of and patient compliance towards the active ingredient/delivery system/packaging trinity should be considered important determinants of therapeutic success.

L138 ANSWER 19 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003092295 EMBASE
TITLE: Noncovalent dimerization of paclitaxel in solution: Evidence from electrospray ionization mass spectrometry.
AUTHOR: Lorenz S.A.; Bigwarfe Jr. P.M.; Balasubramanian S.V.; Fetterly G.J.; Straubinger R.M.; Wood T.D.
CORPORATE SOURCE: T.D. Wood, Department of Chemistry, Natural Sciences Complex, State University of New York, Buffalo, NY 14260-3000, United States. twood@acsu.buffalo.edu
SOURCE: Journal of Pharmaceutical Sciences, (1 Sep 2002) 91/9 (2057-2066).
Refs: 40
ISSN: 0022-3549 CODEN: JPMSAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

SUMMARY LANGUAGE: English
AB Paclitaxel, a unique antimitotic chemotherapy agent that inhibits cell division by binding to microtubules and prevents them from "depolymerizing," has received widespread interest because of its efficacy in fighting certain types of cancer, including breast and ovarian cancer. Paclitaxel undergoes aggregation at millimolar concentrations in both aqueous media and solvents of low polarity (mimicking hydrophobic environments). Its aggregation may have impact on its aqueous stability and its ability to stabilize microtubules. Here, we investigated the dimerization phenomenon of paclitaxel by electrospray ionization mass spectrometry (ESI-MS). Paclitaxel dimers were stable in solutions of acetonitrile/aqueous ammonium acetate (80/20) and aqueous sodium acetate/acetonitrile (92/8 or 95/5) at various pH values. Additional experiments using solution-phase hydrogen/deuterium exchange were employed to ascertain whether or not the observed dimers were formed in solution or as an artifact of the ESI process by ion-molecule reaction. The evidence supports formation of the dimer in solution, and the approach used can be extended to investigation of other types of drug-drug interactions. .COPYRGT. 2002 Wiley-Liss, Inc.

L138 ANSWER 20 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002386597 EMBASE
TITLE: Counterfeit cases set stage for Today's Laws, safety mechanisms.
AUTHOR: Fintor L.
SOURCE: Journal of the National Cancer Institute, (2 Oct 2002) 94/19 (1425).
ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
039 Pharmacy
049 Forensic Science Abstracts
LANGUAGE: English

L138 ANSWER 21 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002216109 EMBASE
TITLE: Use of a cholesterol-rich emulsion that binds to low-density lipoprotein receptors as a vehicle for paclitaxel.
AUTHOR: Rodrigues D.G.; Covolan C.C.; Coradi S.T.; Barboza R.; Maranhao R.C.
CORPORATE SOURCE: R.C. Maranhao, Inst. do Coracao Hosp. Clin. FMUSP, Lab. de Metabolismo de Lipides, Av. Dr. Eneas de Carvalho Aguiar, 44, Andar Sao Paulo - SP 05403-000, Brazil. ramarans@usp.br
SOURCE: Journal of Pharmacy and Pharmacology, (2002) 54/6 (765-772).
Refs: 21
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
030 Pharmacology
016 Cancer
029 Clinical Biochemistry
015 Chest Diseases, Thoracic Surgery and Tuberculosis
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A cholesterol-rich emulsion (LDE) is taken up by malignant cells which over-express low-density lipoprotein (LDL) receptors and thus may be used as a carrier for drugs directed against neoplastic cells. In this study,

we associated the antineoplastic agent paclitaxel to LDE and analysed the new formulation's incorporation efficiency, chemical and physical stability, cellular uptake and cytostatic activity against a neoplastic cell line and the acute toxicity to rats. A paclitaxel incorporation efficiency of approximately 7/5% was achieved when paclitaxel was mixed with LDE at a 6:1 lipid-to-drug molar ratio. The association of paclitaxel with LDE increased by 54% the mean diameter of the emulsion particles but did not damage the paclitaxel chemical structure as analysed by HPLC. Results from gradient ultracentrifugation and Sephadex G25 gel filtration indicated that the binding of the drug to the emulsion was stable. It was shown that the cellular uptake and the cytotoxic activity of LDE-paclitaxel by a neoplastic cell line (NCI-H292 cells) was indeed mediated by the LDL receptors. The anti-proliferative activity of LDE-paclitaxel against NCI-H292 cells was less than that of a commercial paclitaxel preparation (50% inhibitory concentration, IC50 = 2.60 and 0.45 .mu.M, respectively). This difference, however, can be ascribed to the in-vitro anti-proliferative activity of the commercial paclitaxel vehicle Cremophor EL; when Cremophor EL was added to the cultures with LDE-paclitaxel, the IC50 value was reduced to 0.45 .mu.M, attaining that of the commercial paclitaxel preparation. The tolerability of LDE-paclitaxel in rats was remarkable, such that its lethal dose (LD50) was ten-fold greater than that of the commercial formulation (LD50 = 324 and 31.8 mg kg(-1), respectively). Therefore, LDE-paclitaxel association is stable and the cytostatic activity of the drug is preserved while its toxicity to rats is small. By diminishing the side effects and directing paclitaxel to neoplastic tissues, LDE may be useful as adjuvant in chemotherapy with this drug.

L138 ANSWER 22 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003044416 EMBASE
TITLE: HPMA copolymers platinates containing dicarboxylato ligands. Preparation, characterisation and in vitro and in vivo evaluation.
AUTHOR: Gianasi E.; Buckley R.G.; Latigo J.; Wasil M.; Duncan R.
CORPORATE SOURCE: R. Duncan, Centre for Polymer Therapeutics, Welsh School of Pharmacy, King Edward VII Ave, Cardiff CF10 3XF, United Kingdom. duncanr@cf.ac.uk
SOURCE: Journal of Drug Targeting, (2002) 10/7 (549-556).
Refs: 32
ISSN: 1061-186X CODEN: JDTAEH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB N-(2-Hydroxypropyl) methacrylamide (HPMA) copolymer platinates were prepared from polymeric intermediates containing Gly-Phe-Leu-Gly side chains terminating in either malonate or aspartate dicarboxylato ligands. Platinum(II) was bound by reaction of the dicarboxylato ligands with wt% (by AAS). This is close to the theoretical maximum value. The release rate of platinum species in vitro at pH 7.4 correlated with the expected stability of the 6 and 7 membered chelate rings; 14%/24 h platinum released in the case of the malonate and 68%/24 h platinum released in the case of the aspartate. Cisplatin and the aspartate conjugate displayed similar toxicity in vitro against B16F10 and COR-L23 cells while the malonate was at least 8-fold less toxic. The malonate conjugate showed significantly improved activity (T/C = 1.27-1.5) when compared with cisplatin (T/C = 1.18) that was not active when administered intravenously

to treat a subcutaneous B16F10 tumour. The conjugate was at least 20-fold less toxic than cisplatin in vivo. After i.v. administration, the platinum accumulation in B16F10 tumour tissue showed a 19-fold increase in Pt AUC for the malonate conjugate when compared to cisplatin administered equi-dose at its maximum tolerated dose (MTD) (1 mg/kg).

L138 ANSWER 23 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002200255 EMBASE
TITLE: Pilot study of hydrolytically activated paclitaxel prodrug therapy in patients with progressive malignancies.
AUTHOR: Wrasidlo W.; Niethammer A.; Deger S.; Sehouli J.; Kulozik A.; Geilen W.; Henze G.; Gaedicke G.; Lode H.N.
CORPORATE SOURCE: Dr. H.N. Lode, Charite Children's Hospital, Forschungshaus 2.0407, Augustenburgerplatz 1, 13353 Berlin, Germany. holger.lode@charite.de
SOURCE: Current Therapeutic Research - Clinical and Experimental, (2002) 63/4 (247-262).
Refs: 32
ISSN: 0011-393X CODEN: CTCEA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: The development of novel strategies based on chemotherapy with prodrugs is still a challenge for physicians developing effective treatment of malignancies in advanced-stage disease. In this study, we tested the hypothesis that this can be achieved by a prodrug of paclitaxel if the C7 hydroxyl group is blocked by condensation with a solketal chloroformate followed by a ring-opening reaction to the dihydroxyl derivative. Objective: The purpose of this study was to obtain information about toxicity, pharmacokinetic characteristics, and outcomes following paclitaxel prodrug therapy in 10 patients suffering from various progressive end-stage malignancies. Methods: Eligible patients had failed standard therapies and presented with progressive disease, were free of acute infections, had a total white blood cell count >2500 cells/mm(3) and platelet count of >150,000 cells/mm(3), and had received chemo- or radiotherapy in the preceding 8 weeks. Subjects were treated with paclitaxel prodrug (pro Taxol) (100-1200 mg/m(2)) under the compassionate-use Investigational New Drug setting, and toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria (version 2.0). Pharmacokinetic characteristics of paclitaxel prodrug and paclitaxel released from the prodrug were determined by high-performance liquid chromatography. Results: Ten patients with different progressive malignancies were enrolled. Pharmacokinetic monitoring of treated patients demonstrated an increase in the serum half-life (-5-fold, 14.0 hours vs 2.9 hours) and the maximum plasma drug concentration (-50-fold, 110.0 .mu.M vs 2.7 .mu.M) of the paclitaxel prodrug over active paclitaxel, respectively. Furthermore, paclitaxel prodrug was shown to convert to active paclitaxel. The patients tolerated doses of .ltoreq.1200 mg/m(2), with transient liver toxicity starting at 450 mg/m(2). Grade 4 neutropenia was observed in 4 patients and required treatment with granulocyte colony-stimulating factor. Among the 10 enrolled patients, we observed 2 with complete remissions, 3 with partial responses, 1 with stable disease, and 4 with progressive disease. Conclusions: In this study, hydrolytically activated therapy with a paclitaxel prodrug resulted in decreased toxicity in patients based on a slow release of active paclitaxel. Encouraging effects on the course of the disease were observed, albeit in a heterogeneous patient population.

These findings indicate that paclitaxel prodrug may further improve the success rate of chemotherapy with active paclitaxel.

L138 ANSWER 24 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002296695 EMBASE
TITLE: Nanostructured lipid matrices for improved microencapsulation of drugs.
AUTHOR: Muller R.H.; Radtke M.; Wissing S.A.
CORPORATE SOURCE: R.H. Muller, Department of Pharmaceutics, Free University of Berlin, Kelchstr. 31, 12169 Berlin, Germany. mpharma@zedat.fu-berlin.de
SOURCE: International Journal of Pharmaceutics, (21 Aug 2002) 242/1-2 (121-128).
Refs: 35
ISSN: 0378-5173 CODEN: IJPHDE
PUBLISHER IDENT.: S 0378-5173(02)00180-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB At the beginning of the nineties solid lipid nanoparticles (SLN) have been introduced as a novel nanoparticulate delivery system produced from solid lipids. Potential problems associated with SLN such as limited drug loading capacity, adjustment of drug release profile and potential drug expulsion during storage are avoided or minimised by the new generation, the nanostructured lipid carriers (NLC). NLC are produced by mixing solid lipids with spatially incompatible lipids leading to special structures of the lipid matrix, i.e. three types of NLC: (I) the imperfect structured type, (II) the structureless type and (III) the multiple type. A special preparation process-applicable to NLC but also SLN-allows the production of highly concentrated particle dispersions (>30-95%). Potential applications as drug delivery system are described. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

L138 ANSWER 25 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002114052 EMBASE
TITLE: [Production and quality of Paclitaxel injection produced in the hospital pharmacy].
HERSTELLUNG UND ANALYTIK EINES IN DER KRANKENHAUSAPOTHEKE HERGESTELLTEN PACLITAXEL-INFUSIONSLOSUNGSKONZENTRATS.
AUTHOR: Theuer H.; Scherbel G.; Wilken A.; Wendt J.
CORPORATE SOURCE: Dr. H. Theuer, Apotheke Klin. Nurnberg Sud, Breslauer Strasse 201, 90471 Nurnberg, Germany. theuer@klinikum-nuernberg.de
SOURCE: Krankenhauspharmazie, (2002) 23/3 (93-99).
Refs: 27
ISSN: 0173-7597 CODEN: KRANDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: German
SUMMARY LANGUAGE: English; German
AB The production of Paclitaxel injection in the hospital pharmacy represents a very interesting possibility to reduce therapy costs at a high quality level. The composition, production, quality control methods and stability testing of paclitaxel injection are described. We monitored the stability of the injection solution at light protected storage at < -20.degree.C over a period of 12 weeks. The decomposition rate of Paclitaxel at this temperature was very low, so that the amount after this time was 98,63 % of the initial value and the product conforms the specification. The

long-term stability study continues. The quality of the Paclitaxel injection produced in the hospital pharmacy was found to be at the same level as the industrial products.

L138 ANSWER 26 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-058317 [05] WPIDS
DOC. NO. CPI: C2003-014825
TITLE: Composition used for micellar drug delivery vehicles used for treating e.g. cancer, comprises micelle-forming biocompatible diblock copolymer, polymer and/or water soluble, biocompatible organic solvent and hydrophobic drug.
DERWENT CLASS: A96 B07
INVENTOR(S): GUAN, D; LIGGINS, R; MURPHY, L
PATENT ASSIGNEE(S): (GUAN-I) GUAN D; (LIGG-I) LIGGINS R; (MURP-I) MURPHY L; (ANGI-N) ANGIOTECH PHARM INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002072150	A2	20020919	(200305)*	EN	67
US 2003054036	A1	20030320	(200323)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002072150	A2		WO 2002-CA326	20020313
US 2003054036	A1	Provisional	US 2001-275725P	20010313
		Provisional	US 2001-337935P	20011107
			US 2002-99135	20020313

PRIORITY APPLN. INFO: US 2001-337935P 20011107; US 2001-275725P 20010313; US 2002-99135 20020313

AB WO 200272150 A UPAB: 20030121
NOVELTY - Composition comprises:
(a) a micelle-forming biocompatible diblock copolymer having a hydrophilic block comprising residues of monomer, and a hydrophobic block comprising residues of monomer;
(b) an additive comprising polymer and/or a water soluble, biocompatible, organic solvent, and
(c) a hydrophobic drug.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(a) production of the composition which comprises treating the composition according to a sterilization process comprising sterile filtration, sterilization with ethylene oxide or sterilization with ionic radiation;
(b) forming a drug delivery vehicle which comprises adding water to the composition to form a micelle-containing composition;
(c) forming a composition which comprises combining the diblock copolymer, additive and hydrophobic drug with an additional organic (processing) solvent, and removing the organic (processing) solvent by evaporation or distillation, and

(d) preparation of a composition which comprises dissolving a micelle-forming biocompatible diblock copolymer, precipitating or crystallizing the diblock copolymer from the purification solvent, and separating the diblock copolymer from the purification solvent.

ACTIVITY - Cytostatic; Antibacterial; Antiinflammatory; Neuroprotective; Nootropic; Antipsoriatic; Vasotropic; Cardiant.

MECHANISM OF ACTION - None given in the source material.

USE - Used for micellar drug delivery vehicles useful for treating and preventing inflammatory conditions, neurological disorders, cancer, and benign hyperproliferative diseases, particular arthritis, multiple sclerosis, Alzheimer's disease, psoriasis, stenosis or restenosis, benign hyperplasia, cardiovascular disease, inflammatory bowel disease.

ADVANTAGE - The composition forms micelles at an improved rate, have improved ability to incorporate drugs and/or have improved physical properties e.g. viscosity and/or melting point that render the composition easy to make and/or handle.

Dwg.0/0

L138 ANSWER 27 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-732710 [79] WPIDS
DOC. NO. NON-CPI: N2002-577796
DOC. NO. CPI: C2002-207296
TITLE: Implant used for treating vascular narrowing or occlusion, especially for controlling restenosis contains FK506 in chemically bound or physically fixed form.
DERWENT CLASS: A96 B05 B07 D22 P32
INVENTOR(S): VON OEPEN, R; WNENDT, S; KUTTLER, B; LANG, G
PATENT ASSIGNEE(S): (JOME-N) JOMED GMBH
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002065947	A2	20020829	(200279)*	GE	70

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

DE 10107339	A1	20020905	(200279)
DE 10127011	A1	20021212	(200281)
DE 10127330	A1	20021212	(200281)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002065947	A2	WO 2002-EP1707	20020218
DE 10107339	A1	DE 2001-10107339	20010216
DE 10127011	A1	DE 2001-10127011	20010605
DE 10127330	A1	DE 2001-10127330	20010606

PRIORITY APPLN. INFO: DE 2001-10127330 20010606; DE 2001-10107339 20010216; DE 2001-10127011 20010605

AB WO 200265947 A UPAB: 20021209

NOVELTY - Implant (A) contains FK506 in chemically bound (covalent or non-covalent) or physically fixed form and optionally at least one other active agent (II).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) preparation of (A) optionally coated with active agents, and
(b) a stent with a polymeric surface including, in chemically bound (covalent or non-covalent) or physically fixed form, at least one physiologically and/or pharmaceutically active agent.
ACTIVITY - Vasotropic.
MECHANISM OF ACTION - None given in the source material.
USE - (A), particularly stents or stent grafts, are used for treatment and prevention of narrowing or occlusion of coronary or peripheral blood vessels, most especially to prevent restenosis.
ADVANTAGE - The FK506 can be incorporated into stents that have already been sterilized.
Dwg.0/7

L138 ANSWER 28 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-571920 [53] WPIDS
DOC. NO. NON-CPI: N2000-423145
DOC. NO. CPI: C2000-170407
TITLE: Simplified unit-dose **packaging** of medicinal zinc chloride mixtures for the topical treatment of melanoma skin cancer and other skin diseases facilitate zinc chloride treatment and dosage control.
DERWENT CLASS: B05 D22 P32
INVENTOR(S): BROOKS, L S; BROOKS, N A
PATENT ASSIGNEE(S): (BROO-I) BROOKS L S; (BROO-I) BROOKS N A
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000048541	A1	20000824	(200053)*	EN	48

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000029989	A	20000904	(200103)
US 2002081328	A1	20020627	(200245)
US 2002150630	A1	20021017	(200270)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000048541	A1		WO 2000-US4033	20000216
AU 2000029989	A		AU 2000-29989	20000216
US 2002081328	A1	Provisional	US 1999-120656P	19990219
			US 2000-505618	20000216
US 2002150630	A1	Provisional	US 1999-120656P	19990219
		CIP of	US 2000-505618	20000216
			US 2002-171326	20020612

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000029989	A	Based on	WO 200048541

PRIORITY APPLN. INFO: US 1999-120656P 19990219; US 2000-505618 20000216; US 2002-171326 20020612
AB WO 200048541 A UPAB: 20001023
NOVELTY - Unit-dose **packaging** of medicinal zinc chloride mixtures for the topical treatment of melanoma skin cancer and other skin

diseases is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for:

(1) transdermal applicators for use in treating skin diseases;

(2) humectantly (sic) **sealed**, multi-layered, flexible, transdermal applicators for use in treating skin diseases; and

(3) methods for removing abnormal skin growths.

ACTIVITY - Cytostatic; anti-melanoma; dermatological.

USE - The unit-dose **packagings** are used for the topical treatment of melanoma skin cancer and other skin diseases (claimed). They are used to treat human melanoma, basal and squamous cell skin cancer and a variety of other skin tumors and skin diseases such as warts. They may also be use to treat tumors including neoplasms and carcinomas of the parotid gland, bone, larynx, mouth, accessory nasal sinuses, lips, breast and anal region, sarcomas, actnic and seborrheic keratoses, keratoacanthoma, hemangiomas, lymphangiomas, nevi, warts and other epithelial growths, to safely treat skin cancer patients infected with the AIDS virus, to provide a bactericidal effect on infected tissues, to stimulate the angiogenesis of granulation tissue that results in rapid spontaneous wound healing and to heal infected necrotic tissue of diabetic gangrene.

ADVANTAGE - The **packagings** are simplified compared with prior art dressings for holding zinc chloride pastes. They facilitate the use of treatments using zinc chloride and allow the physician to easily control the dosage of zinc chloride administered while maintaining the zinc chloride in an environmentally controlled atmosphere.

DESCRIPTION OF DRAWING(S) - Bottom and side perspective of a transdermal applicator illustrating the removal of a peel-away strip.

transdermal applicator 10

backing 18

zinc chloride mixture 22

adhesive substrate 24

peel-away strip. 26

Dwg.7/13

L138 ANSWER 29 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-302469 [25] WPIDS
DOC. NO. CPI: C1999-088639
TITLE: Use of arsenic compounds for treatment of solid tumors and metastatic neoplastic disease.
DERWENT CLASS: B05 B06
INVENTOR(S): ELLISON, R M; MERMELSTEIN, F H; ELLISON, R
PATENT ASSIGNEE(S): (POLA-N) POLARX BIOPHARMACEUTICALS INC; (ELLI-I) ELLISON R M; (MERM-I) MERMELSTEIN F H
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9918798	A1	19990422	(199925)*	EN	58
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9910893	A	19990503	(199937)		
EP 1022951	A1	20000802	(200038)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
NO 2000001977	A	20000613	(200040)		
BR 9813085	A	20000822	(200050)		
CN 1282218	A	20010131	(200131)		
KR 2001015755	A	20010226	(200156)		
NZ 503973	A	20010928	(200161)		

JP 2001519366 W 20011023 (200202) 52
MX 2000003653 A1 20010701 (200236)
AU 751932 B 20020829 (200264)
US 2002183385 A1 20021205 (200301)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9918798	A1		WO 1998-US21782	19981015
AU 9910893	A		AU 1999-10893	19981015
EP 1022951	A1		EP 1998-953552	19981015
			WO 1998-US21782	19981015
NO 2000001977	A		WO 1998-US21782	19981015
			NO 2000-1977	20000414
BR 9813085	A		BR 1998-13085	19981015
			WO 1998-US21782	19981015
CN 1282218	A		CN 1998-812218	19981015
KR 2001015755	A		KR 2000-703973	20000414
NZ 503973	A		NZ 1998-503973	19981015
			WO 1998-US21782	19981015
JP 2001519366	W		WO 1998-US21782	19981015
			JP 2000-515442	19981015
MX 2000003653	A1		MX 2000-3653	20000414
AU 751932	B		AU 1999-10893	19981015
US 2002183385	A1	Provisional	US 1997-62375P	19971015
			US 1998-173531	19981015

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9910893	A	Based on	WO 9918798
EP 1022951	A1	Based on	WO 9918798
BR 9813085	A	Based on	WO 9918798
NZ 503973	A	Based on	WO 9918798
JP 2001519366	W	Based on	WO 9918798
AU 751932	B	Previous Publ.	AU 9910893
		Based on	WO 9918798

PRIORITY APPLN. INFO: US 1997-62375P 19971015; US 1998-173531 19981015

AB WO 9918798 A UPAB: 20021105
NOVELTY - Solid tumors or metastatic neoplastic disease or hematopoietic disorders are treated by administration of one or more arsenic compounds (I).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(a) treatment of neoplastic diseases in humans comprising administration of (I) or its salt in combination with at least one other therapeutic agent;

(b) an oral pharmaceutical composition useful for treating neoplastic diseases in a human comprising (I) or its salt and a carrier, diluent or excipient; and

(c) a sterile unit dosage form adapted for parenteral administration comprising a non-lethal amount of arsenic trioxide in an aqueous carrier, the dosage form being contained in a **sealed** glass **container**.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - Phosphorous analogue able to interfere with signal transduction in apoptosis; inhibitor of angiogenesis.

USE - The method is particularly useful for treatment of tumors of the epithelial tissue, preferably epithelial glands, epithelial ducts,

liver, biliary tract, gastrointestinal tract, respiratory tract or urogenital tract, lymphoid tissue, connective tissue, bone or central nervous system, metastatic neoplastic diseases of the epithelial tissue, lymphoid tissue, connective tissue, bone or central nervous system. The tumor is preferably a squamous cell carcinoma of the esophagus, adenocarcinoma of esophagus, colorectal carcinoma, gastric carcinoma, Hodgkins lymphoma, non-Hodgkin's lymphoma, follicular lymphoma, diffuse lymphoma, lymphoblastic lymphoma, large cell lymphoma, small lymphocytic lymphoma, neuroblastoma, retinoblastoma, glioblastoma or oligodendroglioma (all claimed).

The compounds are also useful for the treatment of metastatic neoplastic diseases, e.g. primary and metastatic tumors of the central nervous system, refractory primary and metastatic tumors of the central nervous system, breast, lung, bladder and prostate cancer and refractory breast, lung, bladder and prostate cancer.

DESCRIPTION OF DRAWING(S) - The figure is a dose response curve for leukemic cell lines CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226 and SR after continuous exposure to 10-5 to 10-9 mu g/ml arsenic trioxide for 2 days.

Dwg.1a/4

L138 ANSWER 30 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-312193 [26] WPIDS
CROSS REFERENCE: 1996-259556 [26]; 1999-141873 [12]; 1999-141995 [12]; 1999-141996 [12]; 1999-302629 [25]; 2000-269088 [16]
DOC. NO. CPI: C1999-092089
TITLE: Composition for the treatment of cancer.
DERWENT CLASS: B05
INVENTOR(S): HARIDAS, K; HAUSHEER, F H; MURALI, D; PEDDAIAHGARI, S; REDDY, D G
PATENT ASSIGNEE(S): (BION-N) BIONUMERIK PHARM INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5902610	A	19990511	(199926)*		24

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5902610	A	CIP of	US 1994-338379	19941114
			US 1995-553005	19951103

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5902610	A	CIP of	US 5789000

PRIORITY APPLN. INFO: US 1995-553005 19951103; US 1994-338379 19941114

AB US 5902610 A UPAB: 20011211

NOVELTY - Composition comprising 2,2'-dithio-bis-ethane sulfonate (DBES), cis-diamine dichloro platinum (cisplatin), sodium chloride, and an **acid** selected from hydrochloric **acid** and phosphoric **acid**.

DETAILED DESCRIPTION - Composition comprising:

(a) 0.1-1.0 mg/ml DBES;
(b) 100-300 mg/ml cisplatin;
(c) 0.1-2.5 wt. % sodium chloride; and
(d) hydrochloric **acid** and/or phosphoric **acid**, in

amount to maintain the pH at 2.0-6.0.

An INDEPENDENT CLAIM is also included for reducing the toxic effects of cisplatin, by administration of DBES, or one of it's salts.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - None given.

USE - The composition is used for the treatment of cancer.

ADVANTAGE - The DBES reduces the toxicity, especially bone-marrow induced toxicity, in vivo associated with the use of cisplatin (claimed). The composition also exhibits synergistic activity.

DBES was administered at 1000 mg/kg to Fischer rats receiving a nephrotoxic dose of cisplatin (6 mg/kg). The composition gave 100 % protection against toxicity, as assessed by creatinine levels.

Dwg.0/5

L138 ANSWER 31 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1994-199826 [24] WPIDS
CROSS REFERENCE: 1994-199827 [24]; 1994-199957 [24]
DOC. NO. CPI: C1994-091240
TITLE: Injectable antineoplastic **taxol** compsns. with improved stability - contain **taxol** in polyethoxylated castor oil adjusted to pH below 8.1.
DERWENT CLASS: A96 B02 P12 P33
INVENTOR(S): CARVER, D; ELLIOTT, R L; EWALD, H; HANDRECK, G P; PROUT, T; CARVER, D R; PROUT, T R; ELLIOTT, R; HANDRECK, P
PATENT ASSIGNEE(S): (FAUL-N) FAULDING & CO LTD F H; (FAUL-N) FAULDING F H & CO LTD; (NAPR-N) NAPRO BIOTHERAPEUTICS INC; (NAPR-N) NAPRO BIO THERAPEUTICS INC
COUNTRY COUNT: 45
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9412030	A1	19940609	(199424)*		9
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE					
W: AU BB BG BR CA CZ FI HU JP KP KR KZ LK MG MN MW NO NZ RO RU SD SK UA UZ					
AU 9351967	A	19940609	(199428)		
AU 9456126	A	19940622	(199436)		
ZA 9308844	A	19940928	(199440)		8
CN 1095266	A	19941123	(199546)		
NZ 258044	A	19951221	(199606)		
AU 667142	B	19960307	(199617)		
CN 1096673	A	19941228	(199719)		
EP 835657	A1	19980415	(199819)	EN	7
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
US 5733888	A	19980331	(199820)		4
ES 2119996	T3	19981016	(199849)		
US 5972992	A	19991026	(199952)		
US 5977164	A	19991102	(199953)		
CA 2308082	A1	19940609	(200048)	EN	
US 6140359	A	20001031	(200057)		
US 6306894	B1	20011023	(200165)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9412030	A1	WO 1993-US11199	19931118
AU 9351967	A	AU 1993-51967	19931125
AU 9456126	A	AU 1994-56126	19931118
ZA 9308844	A	ZA 1993-8844	19931126
CN 1095266	A	CN 1993-120529	19931127
NZ 258044	A	NZ 1993-258044	19931125

AU 667142	B		AU 1993-51967	19931125
CN 1096673	A		CN 1993-115293	19931126
EP 835657	A1	Div ex	EP 1994-901593	19931118
			EP 1997-121710	19931118
US 5733888	A	Cont of	US 1992-995501	19921222
			US 1996-594478	19960131
ES 2119996	T3		EP 1994-901593	19931118
US 5972992	A	Cont of	US 1992-995501	19921222
		Cont of	US 1996-594478	19960131
			US 1998-28906	19980224
US 5977164	A	Div ex	US 1996-594478	19960131
			US 1997-979836	19971126
CA 2308082	A1	Div ex	CA 1993-2149150	19931118
			CA 1993-2308082	19931118
US 6140359	A	Cont of	US 1992-995501	19921222
		Div ex	US 1996-594478	19960131
		Div ex	US 1997-979836	19971126
			US 1999-356158	19990719
US 6306894	B1	Cont of	US 1992-995501	19921222
		Div ex	US 1996-594478	19960131
		Cont of	US 1997-979836	19971126
		Cont of	US 1999-356158	19990719
			US 2000-563969	20000503

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9456126	A	Based on	WO 9412030
AU 667142	B	Previous Publ.	AU 9351967
EP 835657	A1	Div ex	EP 674510
ES 2119996	T3	Based on	EP 674510
US 5972992	A	Cont of	US 5733888
US 5977164	A	Div ex	US 5733888
US 6140359	A	Div ex	US 5733888
US 6306894	B1	Div ex	US 5733888
		Cont of	US 5977164
		Cont of	US 6140359

PRIORITY APPLN. INFO: US 1992-995501 19921222; AU 1992-6074 19921127

AB WO 9412030 A UPAB: 20011108

Compsn. consisting of **taxol** in a polyethoxylated castor oil has a pH less than 8.1

Acid is mixed with a polyethoxylated castor oil carrier material to form a first carrier soln. and then mixing **taxol** with this soln. to form a **taxol** soln. of pH less than 8.1. The **acid** is acetic **acid** or citric **acid**.

USE/ADVANTAGE - The injectable composition is antineoplastic with good cytotoxic activity against IP implanted D16 melanoma and the human X-1 mammary tumour xenograft. **Taxol** has good response rates in treating both ovarian and breast cancer patients who were not benefiting from vinca alkaloid or cisplatin therapy and has shown encouraging results in patients with other types of cancer including lung, melanoma, lymphoma, head and neck. The **taxol** composition has a lower pH than known formulations resulting in greater stability and longer shelf life than the known formulations. The **taxol** does not readily degrade.

In an example, a soln. was prepd. with the following formulation 0.5 ml Cremophor El, 2.0 mg citric **acid** (anhydrous), 6.0 mg **taxol**, and absolute alcohol to 1.0 ml. The pH of this soln. was 6.1. The stability of this sample was compared to that of a similar sample contg. no **acid** and of pH 9.1. The solns. were stored at 40 deg.C for 7 days in glass 5 ml **vials sealed** with rubber

bungs. After storage the pH of the 2 samples was 6.2 and 9.0, the potency was 96.6% and 86.7% the major individual impurity was 0.3% and 5.1% and the total impurities was 2.0% and 12.2%.
Dwg.0/0

FILE 'HOME' ENTERED AT 12:42:15 ON 10 APR 2003

=> fil reg; d stat que l8
FILE 'REGISTRY' ENTERED AT 12:38:05 ON 10 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 9 APR 2003 HIGHEST RN 502545-60-0
DICTIONARY FILE UPDATES: 9 APR 2003 HIGHEST RN 502545-60-0

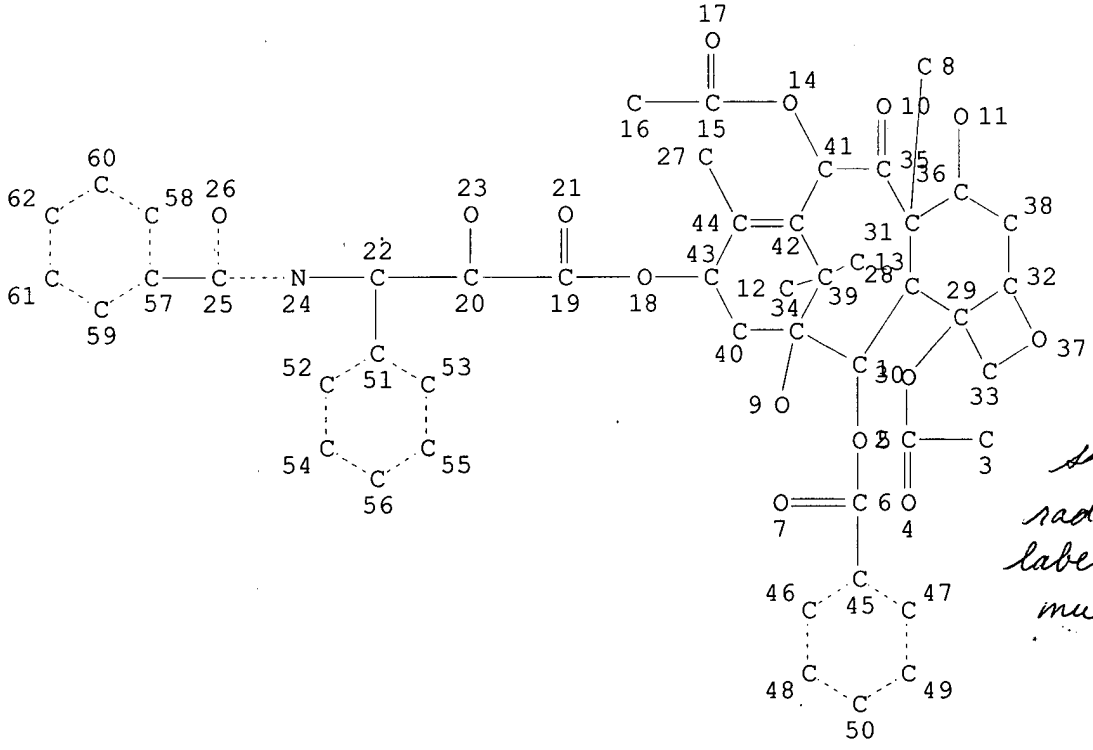
TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L6 STR



paclitaxel

family search done to find salts, stereoisomers, radioisotopically labelled forms, & multicomponent substances

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L8 71 SEA FILE=REGISTRY FAM FUL L6

100.0% PROCESSED 1348 ITERATIONS 71 ANSWERS
SEARCH TIME: 00.00.01

=> fil capl; d que nos l23; d que nos l28; d que nos l34

FILE 'CAPLUS' ENTERED AT 12:38:05 ON 10 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 10 Apr 2003 VOL 138 ISS 15
FILE LAST UPDATED: 9 Apr 2003 (20030409/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L6		STR
L8	71	SEA FILE=REGISTRY FAM FUL L6
L9	1	SEA FILE=REGISTRY ABB=ON ETHANOL/CN
L10	1	SEA FILE=REGISTRY ABB=ON CITRIC ACID/CN
L11	1	SEA FILE=REGISTRY ABB=ON ACETIC ACID/CN
L12	20	SEA FILE=REGISTRY ABB=ON CASTOR OIL, ETHOXYLATED?/CN
L13	7488	SEA FILE=CAPLUS ABB=ON (PACLITAXEL OR TAXOL)/OBI
L14	6976	SEA FILE=CAPLUS ABB=ON L8
L15	191380	SEA FILE=CAPLUS ABB=ON L9 OR (ETHANOL OR ETOH OR ETHYL ALCOHOL)/OBI
L16	46244	SEA FILE=CAPLUS ABB=ON L10 OR (CITRIC ACID)/OBI
L17	147274	SEA FILE=CAPLUS ABB=ON L11 OR ACETIC ACID/OBI
L18	1	SEA FILE=REGISTRY ABB=ON CASTOR OIL/CN
L19	2891	SEA FILE=CAPLUS ABB=ON (L18 OR CASTOR OIL/CT)(L)?ETHOXYLAT?
L20	43	SEA FILE=CAPLUS ABB=ON L12
L23	10	SEA FILE=CAPLUS ABB=ON (L13 OR L14) AND (L19 OR L20) AND (L16 OR L17) AND L15

L6		STR
L8	71	SEA FILE=REGISTRY FAM FUL L6
L9	1	SEA FILE=REGISTRY ABB=ON ETHANOL/CN
L10	1	SEA FILE=REGISTRY ABB=ON CITRIC ACID/CN
L11	1	SEA FILE=REGISTRY ABB=ON ACETIC ACID/CN
L12	20	SEA FILE=REGISTRY ABB=ON CASTOR OIL, ETHOXYLATED?/CN
L13	7488	SEA FILE=CAPLUS ABB=ON (PACLITAXEL OR TAXOL)/OBI
L14	6976	SEA FILE=CAPLUS ABB=ON L8
L15	191380	SEA FILE=CAPLUS ABB=ON L9 OR (ETHANOL OR ETOH OR ETHYL ALCOHOL)/OBI

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L16        46244 SEA FILE=CAPLUS ABB=ON  L10 OR (CITRIC ACID)/OBI
L17       147274 SEA FILE=CAPLUS ABB=ON  L11 OR ACETIC ACID/OBI
L18            1 SEA FILE=REGISTRY ABB=ON  CASTOR OIL/CN
L19         2891 SEA FILE=CAPLUS ABB=ON  (L18 OR CASTOR OIL/CT)(L)?ETHOXYLAT?
L20           43 SEA FILE=CAPLUS ABB=ON  L12
L26        50056 SEA FILE=CAPLUS ABB=ON  STOR?(5A)STAB?
L28            4 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND L26 AND ((L15 OR L16
                 OR L17) OR (L19 OR L20))


L6               STR
L8            71 SEA FILE=REGISTRY FAM FUL L6
L9             1 SEA FILE=REGISTRY ABB=ON  ETHANOL/CN
L10            1 SEA FILE=REGISTRY ABB=ON  CITRIC ACID/CN
L11            1 SEA FILE=REGISTRY ABB=ON  ACETIC ACID/CN
L12           20 SEA FILE=REGISTRY ABB=ON  CASTOR OIL, ETHOXYLATED?/CN
L13         7488 SEA FILE=CAPLUS ABB=ON  (PACLITAXEL OR TAXOL)/OBI
L14         6976 SEA FILE=CAPLUS ABB=ON  L8
L15       191380 SEA FILE=CAPLUS ABB=ON  L9 OR (ETHANOL OR ETOH OR ETHYL
                 ALCOHOL)/OBI
L16        46244 SEA FILE=CAPLUS ABB=ON  L10 OR (CITRIC ACID)/OBI
L17       147274 SEA FILE=CAPLUS ABB=ON  L11 OR ACETIC ACID/OBI
L18            1 SEA FILE=REGISTRY ABB=ON  CASTOR OIL/CN
L19         2891 SEA FILE=CAPLUS ABB=ON  (L18 OR CASTOR OIL/CT)(L)?ETHOXYLAT?
L20           43 SEA FILE=CAPLUS ABB=ON  L12
L29         7692 SEA FILE=CAPLUS ABB=ON  STABILIZING AGENTS/CT
L30       124431 SEA FILE=CAPLUS ABB=ON  DRUG DELIVERY SYSTEMS+OLD/CT
L34            7 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND L29 AND ((L15 OR L16
                 OR L17) OR (L19 OR L20)) AND L30

=> s l23 or l28 or l34

L130          17 L23 OR L28 OR L34

=> fil medl; d que l59; d que l60; d que l65

FILE 'MEDLINE' ENTERED AT 12:38:07 ON 10 APR 2003

  FILE LAST UPDATED: 9 APR 2003 (20030409/UP).  FILE COVERS 1958 TO DATE.

  On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

  MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
  MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/summ2003.html
  for a description on changes.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L53          416 SEA FILE=MEDLINE ABB=ON  CASTOR OIL/CT
L59            3 SEA FILE=MEDLINE ABB=ON  L50 AND L53


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L51         4122 SEA FILE=MEDLINE ABB=ON  CITRIC ACID/CT
L52         3074 SEA FILE=MEDLINE ABB=ON  ACETIC ACID/CT
L60            1 SEA FILE=MEDLINE ABB=ON  L50 AND (L51 OR L52)
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L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L54        45703 SEA FILE=MEDLINE ABB=ON  ETHANOL/CT
L62        24525 SEA FILE=MEDLINE ABB=ON  L54(L)(PD OR AD OR PK OR TU)/CT
L64          383 SEA FILE=MEDLINE ABB=ON  CREMOPHOR EL = castor oil
L65            5 SEA FILE=MEDLINE ABB=ON  L50 AND L62 AND L64
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Subheadings
PD = pharmacology
AD = administration & dosage
PK = pharmacokinetics
TU = Therapeutic use

```
=> s l59 or l60 or l65

L131           9 L59 OR L60 OR L65

=> fil embase

FILE 'EMBASE' ENTERED AT 12:38:08 ON 10 APR 2003
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  FILE COVERS 1974 TO 3 Apr 2003 (20030403/ED)

  EMBASE has been reloaded. Enter HELP RLOAD for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> d que l85

L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L71        76078 SEA FILE=EMBASE ABB=ON  ALCOHOL/CT
L74          137 SEA FILE=EMBASE ABB=ON  RICINOMACROGOL/CT
L75          893 SEA FILE=EMBASE ABB=ON  CASTOR OIL/CT
L76          728 SEA FILE=EMBASE ABB=ON  CREMOPHOR/CT
L82        81481 SEA FILE=EMBASE ABB=ON  "CARBOXYLIC ACIDS AND THEIR DERIVATIVES
                 "+NT/CT
L85            2 SEA FILE=EMBASE ABB=ON  L70 AND (L74 OR L75 OR L76) AND (L82
                 OR L71)

=> fil drugu; d que l96; d que l97; d que l112

FILE 'DRUGU' ENTERED AT 12:38:09 ON 10 APR 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE LAST UPDATED: 8 APR 2003       <20030408/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L91       166684 SEA FILE=DRUGU ABB=ON  ACID#
L93         1316 SEA FILE=DRUGU ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L94         2445 SEA FILE=DRUGU ABB=ON  ETHANOL/CT
L96            0 SEA FILE=DRUGU ABB=ON  L90 AND L91 AND L93 AND L94
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L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L91       166684 SEA FILE=DRUGU ABB=ON  ACID#
L92         7449 SEA FILE=DRUGU ABB=ON  (CITRIC OR ACETIC)(W)L91
L93         1316 SEA FILE=DRUGU ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L97            0 SEA FILE=DRUGU ABB=ON  L90 AND L93 AND L92


L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L91       166684 SEA FILE=DRUGU ABB=ON  ACID#
L92         7449 SEA FILE=DRUGU ABB=ON  (CITRIC OR ACETIC)(W)L91
L93         1316 SEA FILE=DRUGU ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L94         2445 SEA FILE=DRUGU ABB=ON  ETHANOL/CT
L98        11741 SEA FILE=DRUGU ABB=ON  STOR###
L99        70702 SEA FILE=DRUGU ABB=ON  STAB?
L111           9 SEA FILE=DRUGU ABB=ON  L90 AND (L91 OR L92 OR L93 OR L94) AND
                 L98 AND L99
L112           8 SEA FILE=DRUGU ABB=ON  L111 NOT (STORY OR STORIES OR STORIED)

=> fil wpids; d que l120

FILE 'WPIDS' ENTERED AT 12:38:10 ON 10 APR 2003
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FILE LAST UPDATED:          7 APR 2003      <20030407/UP>
MOST RECENT DERWENT UPDATE:     200323        <200323/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

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    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L113        1452 SEA FILE=WPIDS ABB=ON  PACLITAXEL OR TAXOL
L114       62094 SEA FILE=WPIDS ABB=ON  ETHANOL OR ETOH OR ETHYL ALCOHOL
L115      813664 SEA FILE=WPIDS ABB=ON  ACID#
L116       50315 SEA FILE=WPIDS ABB=ON  (CITRIC OR ACETIC)(W)L115
L117        5677 SEA FILE=WPIDS ABB=ON  CASTOR OIL# OR RICINOMACROGOL OR
                 CREMOPHOR
L120           5 SEA FILE=WPIDS ABB=ON  L113 AND L116 AND L117 AND L114

=> dup rem l131,l112,l130,l85,l120
FILE 'MEDLINE' ENTERED AT 12:39:12 ON 10 APR 2003

FILE 'DRUGU' ENTERED AT 12:39:12 ON 10 APR 2003
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FILE 'CAPLUS' ENTERED AT 12:39:12 ON 10 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'EMBASE' ENTERED AT 12:39:12 ON 10 APR 2003

FILE 'WPIDS' ENTERED AT 12:39:12 ON 10 APR 2003

PROCESSING COMPLETED FOR L131
PROCESSING COMPLETED FOR L112
PROCESSING COMPLETED FOR L130
PROCESSING COMPLETED FOR L85
PROCESSING COMPLETED FOR L120
L132 38 DUP REM L131 L112 L130 L85 L120 (3 DUPLICATES REMOVED)
ANSWERS '1-9' FROM FILE MEDLINE
ANSWERS '10-17' FROM FILE DRUGU
ANSWERS '18-34' FROM FILE CAPLUS
ANSWER '35' FROM FILE EMBASE
ANSWERS '36-38' FROM FILE WPIDS

=> d ibib ab hitrn 1-38

L132 ANSWER 1 OF 38 MEDLINE
ACCESSION NUMBER: 2002276315 MEDLINE
DOCUMENT NUMBER: 22000994 PubMed ID: 12006516
TITLE: Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel.
AUTHOR: Ibrahim Nuhad K; Desai Neil; Legha Sewa; Soon-Shiong Patrick; Theriault Richard L; Rivera Edgardo; Esmaeli Bita; Ring Sigrid E; Bedikian Agop; Hortobagyi Gabriel N; Ellerhorst Julie A
CORPORATE SOURCE: Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.
SOURCE: CLINICAL CANCER RESEARCH, (2002 May) 8 (5) 1038-44. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020518
Last Updated on STN: 20021018
Entered Medline: 20021017

AB PURPOSE: ABI-007 is a novel Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. The absence of Cremophor EL may permit ABI-007 to be administered without the premedications used routinely for the prevention of hypersensitivity reactions. Furthermore, this novel formulation permits a higher paclitaxel concentration in solution and, thus, a decreased infusion volume and time. This Phase I study examines the toxicity profile, maximum tolerated dose (MTD), and pharmacokinetics of ABI-007. EXPERIMENTAL DESIGN: ABI-007 was administered in the outpatient setting, as a 30-min infusion without premedications. Doses of ABI-007 ranged from 135 (level 0) to 375 mg/m2 (level 3). Sixteen patients participated in pharmacokinetic studies. RESULTS: Nineteen patients were treated. No acute hypersensitivity reactions were observed during the infusion period. Hematological toxicity was mild and not cumulative. Dose-limiting toxicity, which occurred in 3 of 6 patients treated at level 3 (375 mg/m2), consisted of sensory neuropathy (3 patients), stomatitis (2 patients), and superficial keratopathy (2 patients). The MTD was thus determined to be 300 mg/m2 (level 2).

Pharmacokinetic analyses revealed paclitaxel C(max) and area under the curve(inf) values to increase linearly over the ABI-007 dose range of 135-300 mg/m2. C(max) and area under the curve(inf) values for individual patients correlated well with toxicity. CONCLUSIONS: ABI-007 offers several features of clinical interest, including rapid infusion rate, absence of requirement for premedication, and a high paclitaxel MTD. Our results provide support for Phase II trials to determine the antitumor activity of this drug.

L132 ANSWER 2 OF 38 MEDLINE
ACCESSION NUMBER: 2001699031 MEDLINE
DOCUMENT NUMBER: 21610136 PubMed ID: 11745194
TITLE: Intraarterial chemotherapy with polyoxyethylated castor oil free paclitaxel, incorporated in albumin nanoparticles (ABI-007): Phase II study of patients with squamous cell carcinoma of the head and neck and anal canal: preliminary evidence of clinical activity.
AUTHOR: Damascelli B; Cantu G; Mattavelli F; Tamplenizza P; Bidoli P; Leo E; Dosio F; Cerrotta A M; Di Tolla G; Frigerio L F; Garbagnati F; Lanocita R; Marchiano A; Patelli G; Spreafico C; Ticha V; Vespro V; Zunino F
CORPORATE SOURCE: Department of Radiology, Istituto Nazionale Tumori, Milano, Italy.. damascelli@istitutotumori.mi.it
SOURCE: CANCER, (2001 Nov 15) 92 (10) 2592-602.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011219
Last Updated on STN: 20020125
Entered Medline: 20020104

AB BACKGROUND: This study was designed to determine the feasibility, maximum tolerated dose, and toxicities of intraarterial administration of paclitaxel-albumin nanoparticles in patients with advanced head and neck and recurrent anal canal squamous cell carcinoma. Antitumor activity also was assessed. METHODS: Forty-three patients (31 with advanced head and neck and 12 with recurrent anal canal squamous cell carcinoma) were treated intraarterially with ABI-007 every 4 weeks for 3 cycles. In total, 120 treatment cycles were completed, 86 in patients with head and neck carcinoma (median, 3 cycles; range, 1-4) and 34 in patients with anal canal carcinoma (median, 3 cycles; range, 1-4). ABI-007 was compared preliminarily with Taxol for in vitro cytostatic activity. Increasing dose levels from 120 to 300 mg/m2 were studied in 18 patients. Pharmacokinetic profiles after intraarterial administration were obtained in a restricted number of patients. RESULTS: The dose-limiting toxicity of ABI-007 was myelosuppression consisting of Grade 4 neutropenia in 3 patients. Nonhematologic toxicities included total alopecia (30 patients), gastrointestinal toxicity (3 patients, Grade 2), skin toxicity (5 patients, Grade 2), neurologic toxicity (4 patients, Grade 2) ocular toxicity (1 patient, Grade 2), flu-like syndrome (7 patients, Grade 2; 1 patient, Grade 3). In total, 120 transfemoral, percutaneous catheterization procedure-related complications occurred only during catheterization of the neck vessels in 3 patients (2 TIA, 1 hemiparesis) and resolved spontaneously. CONCLUSIONS: Intraarterial administration of ABI-007 by percutaneous catheterization does not require premedication, is easy and reproducible, and has acceptable toxicity. The maximum tolerated dose in a single administration was 270 mg/m2. Most dose levels showed considerable antitumor activity (42 assessable patients with 80.9% complete response and partial response). The recommended Phase II dose is

230 mg/m2 every 3 weeks.

L132 ANSWER 3 OF 38 MEDLINE
ACCESSION NUMBER: 2001217067 MEDLINE
DOCUMENT NUMBER: 21134777 PubMed ID: 11237379
TITLE: Phase I trial and pharmacological study of a 3-hour paclitaxel infusion in children with refractory solid tumours: a SFOP study.
AUTHOR: Doz F; Gentet J C; Pein F; Frappaz D; Chastagner P; Moretti S; Vassal G; Arditti J; Tellingen O V; Iliadis A; Catalin J
CORPORATE SOURCE: Departement d'Oncologie Pediatrique, Institut Curie, 26 rue d'Ulm, Paris, 75231 Cx 05, France.
SOURCE: BRITISH JOURNAL OF CANCER, (2001 Mar 2) 84 (5) 604-10.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB The maximum tolerated dose of paclitaxel administered by 24-hour continuous infusion in children is known. Short infusion might offer equivalent antitumour efficacy and reduced haematological toxicity, without increasing the allergic risk. Our aims were to determine the maximum tolerated dose and the pharmacokinetics of paclitaxel in children when administered in 3-h infusion every 3 weeks. Patients older than 6 months, younger than 20 years with refractory malignant solid tumours were eligible when they satisfied standard haematological, renal, hepatic and cardiologic inclusion criteria with life expectancy exceeding 8 weeks. Paclitaxel was administered as a 3-hour infusion after premedication (dexamethasone, dexchlorpheniramine). Pharmacokinetic analysis and solvent assays (ethanol, cremophor) were performed during the first course. 20 courses were studied in 17 patients; 4 dosage levels were investigated (240 to 420 mg/m(2)). No dose-limiting haematological toxicity was observed. Severe acute neurological and allergic toxicity was encountered. One treatment-related death occurred just after the infusion at the highest dosage. Delayed peripheral neurotoxicity and moderate allergic reactions were also encountered. Pharmacokinetic analysis showed dose-dependent clearance of paclitaxel and elevated blood ethanol and **Cremophor EL** levels. Although no limiting haematological toxicity was reached, we do not recommend this paclitaxel schedule in children because of its acute neurological toxicity.

L132 ANSWER 4 OF 38 MEDLINE
ACCESSION NUMBER: 1998379918 MEDLINE
DOCUMENT NUMBER: 98379918 PubMed ID: 9716061
TITLE: Effects of Taxol on blood cells.
AUTHOR: Shimomura T; Fujiwara H; Ikawa S; Kigawa J; Terakawa N
SOURCE: LANCET, (1998 Aug 15) 352 (9127) 541-2.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917

Entered Medline: 19980908

L132 ANSWER 5 OF 38 MEDLINE
ACCESSION NUMBER: 1998338132 MEDLINE
DOCUMENT NUMBER: 98338132 PubMed ID: 9673415
TITLE: Cell line and schedule-dependent cytotoxicity of paclitaxel (Taxol): role of the solvent **Cremophor EL** /ethanol.
AUTHOR: Cordes N; Plasswilm L
CORPORATE SOURCE: Department of Radiation-Oncology, University Hospitals, Erlangen-Nuernberg, Germany.
SOURCE: ANTICANCER RESEARCH, (1998 May-Jun) 18 (3A) 1851-7. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980810

AB BACKGROUND: Paclitaxel's optimal dosage and scheduling is currently not determined. To compare paclitaxel (PTX) cytotoxicity in vitro, three cell lines were chosen for investigation by single versus fractionated exposure to Taxol and the diluent **Cremophor EL**/ethanol (CEL/eth). METHODS: An exponentially growing human lung-carcinoma (SK-LU-1), human glioblastoma (U-138 MG) and mammalian fibroblast cell line (HyB14FAF28) were used for colony forming assay examining cell survival, and flow cytometric DNA analysis by measuring cell cycle development. Tested concentrations varied from 2-50 microM and were incubated for 3 and 15 hours. Single (2-50 microM/d, especially 10 microM/d), versus fractionated (2 microM/d, day 1-5) exposure of Taxol and CEL/eth was investigated. As the control population, cells were exposed to a phosphate buffered solution (PBS). RESULTS: Control populations demonstrated an average survival of 90, 99 and 93% for SK-LU-1, U-138 MG, B14, respectively. Single Taxol exposure at 10 microM showed average survival of 54, 50 and 84% after 3 hours and 9, 48 and 82% after 15 hours for the above cell lines. Fractionated Taxol exposure with 2 microM/d, days 1-5 led to average survival of 55, 86 and 63%, respectively. Single CEL/eth exposure showed a cytotoxic effect with average survival of 94, 126 and 91% after 3 hours and 47, 63 and 88% after 15 hours respectively. Fractionated CEL/eth exposure showed an average survival of 67, 94 and 65% respectively. Flow cytometric analysis detected cell cycle shift concerning S- and G2/M-phase after Taxol exposure only in the two tumour cell lines, and not in the fibroblastic cells. CEL/eth was without significant effect on cell cycle distribution in all three cell lines. CONCLUSIONS: In the two human tumour cell lines cytotoxicity was more pronounced after prolonged Taxol exposure. The fibroblast cell line was not sensitive to single treatment, and was without cell cycle changes. Comparable to Taxol the diluent CEL/eth had a significant but less pronounced cytotoxic effect. Therefore, the cytotoxic mechanisms of paclitaxel's and CEL/eth's are worthy of further investigation.

L132 ANSWER 6 OF 38 MEDLINE
ACCESSION NUMBER: 1998124724 MEDLINE
DOCUMENT NUMBER: 98124724 PubMed ID: 9463563
TITLE: Cytotoxicity of fractionated paclitaxel (Taxol) administration in vitro.
AUTHOR: Plasswilm L; Cordes N; Fietkau R; Sauer R
CORPORATE SOURCE: Department of Radiooncology, University Erlangen-Nurnberg, Germany.
SOURCE: STRAHLENTHERAPIE UND ONKOLOGIE, (1998 Jan) 174 (1) 37-42. Journal code: 8603469. ISSN: 0179-7158.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980226

AB PURPOSE: Paclitaxel (Taxol) is a new anticancer agent with a novel mechanism of action. It has demonstrated broad clinical activity in a variety of malignancies. Several aspects of paclitaxel's usage remain to be clarified, including the optimal treatment schedule. Furthermore, the diluent of paclitaxel, **Cremophor EL**/ethanol, alone has shown to be markedly active in tumor samples. MATERIAL AND METHODS: The in-vitro cytotoxicity of paclitaxel (Taxol) due to single dose (1 x 10 microM/day, day 1 incubation time: 3 h and 15 h) and fractionated exposure (5 x 2 microM/day, day 1 to 5 incubation time: 3 h/day) was evaluated, measuring surviving fraction (clonogenic assay) and DNA distribution (flow cytometric analysis). In the control population, the diluent **Cremophor EL**/ethanol or a phosphate buffered salt solution (PBS) were applied using identical doses and schedules. A mammalian fibroblast cell line (HyB14FAF28) was used. RESULTS: Fractionated application of paclitaxel (Taxol) produced a significant lower clonogenic survival (0.63) in comparison with single dose exposure for 3 h (0.84) and 15 h (0.82). DNA analysis showed no evidence for a significant difference in DNA distribution of the paclitaxel-specific G2/M phase over a 10-day period. Controls with the diluent **Cremophor EL**/ethanol showed a clonogenic survival of 0.87 (3 h exposure) and 0.88 (15 h exposure) versus 0.65 after fractionated drug administration (5 x 2 microM/day, day 1 to 5, incubation time: 3 h/day). PBS controls and untreated controls did not show any significant effect. CONCLUSIONS: It seems that clonogenic survival after Taxol exposure of this mammalian fibroblast cell line varies with treatment schedule through a yet unknown process that does not involve G2/M arrest. The results indicate the treatment effects to be mainly based on the diluent combination without any further benefit induced by paclitaxel.

L132 ANSWER 7 OF 38 MEDLINE
ACCESSION NUMBER: 96176895 MEDLINE
DOCUMENT NUMBER: 96176895 PubMed ID: 8599876
TITLE: Plasma alcohol concentrations in patients following paclitaxel infusion.
AUTHOR: Webster L K; Crinis N A; Morton C G; Millward M J
CORPORATE SOURCE: Division of Research, Peter MacCallum Cancer Institute, Melbourne, Australia.
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (1996) 37 (5) 499-501.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960513
Last Updated on STN: 19980206
Entered Medline: 19960501

AB Paclitaxel is formulated in 50% **Cremophor El** and 50% ethanol such that patients receiving paclitaxel also receive a significant amount of each of these solvents. The aim of this study was to measure the plasma alcohol levels in patients treated with paclitaxel. A total of 12 patients who were enrolled in phase II trials of non-small-cell lung

cancer, breast cancer or ovarian cancer received 175 mg/m2 paclitaxel given as a 3-h infusion. Blood samples were obtained prior to and immediately following the infusion, and plasma ethanol concentrations were measured enzymatically. The dose of ethanol delivered with the paclitaxel ranged from 20.0 to 28.9 ml. No alcohol was detected in pre-dose plasma, but 8 of 12 patients had detectable levels in post-infusion plasma, with 0.033 g/dl being the highest concentration. The elimination rate of alcohol approximates the infusion rate when paclitaxel is given over 3h, resulting in low or undetectable levels in most patients. However, in patients receiving an equivalent dose of paclitaxel given as a 1-h infusion, the plasma alcohol levels will likely be high enough for significant pharmacological effects to occur.

L132 ANSWER 8 OF 38 MEDLINE
ACCESSION NUMBER: 97086521 MEDLINE
DOCUMENT NUMBER: 97086521 PubMed ID: 8932715
TITLE: Taxol from Pestalotiopsis microspora, an endophytic fungus of Taxus wallachiana.
AUTHOR: Strobel G; Yang X; Sears J; Kramer R; Sidhu R S; Hess W M
CORPORATE SOURCE: Department of Plant Pathology, Montana State University, Bozeman 59717, USA.
CONTRACT NUMBER: 1 ROI CA 58315-03 (NCI)
SOURCE: MICROBIOLOGY, (1996 Feb) 142 (Pt 2) 435-40.
Journal code: 9430468. ISSN: 1350-0872.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19990129
Entered Medline: 19961231
AB Pestalotiopsis microspora was isolated from the inner bark of a small limb of Himalayan yew, Taxus wallachiana, and was shown to produce taxol in mycelial culture. Taxol was identified by spectroscopic and chromatographic comparisons with authentic taxol. Optimal taxol production occurred after 2-3 weeks in still culture at 23 degrees C. [14C]Acetate and [14C]phenylalanine served as precursors for fungal [14C]taxol. These observations on P. microspora are discussed in relation to the biological importance of taxol production by fungi in general.

L132 ANSWER 9 OF 38 MEDLINE
ACCESSION NUMBER: 94361874 MEDLINE
DOCUMENT NUMBER: 94361874 PubMed ID: 7915908
TITLE: Paclitaxel-induced cytotoxicity--the effects of **cremophor EL** (castor oil) on two human breast cancer cell lines with acquired multidrug resistant phenotype and induced expression of the permeability glycoprotein.
COMMENT: Erratum in: Eur J Cancer 1994;30A(6):896
AUTHOR: Fjallskog M L; Frii L; Bergh J
CORPORATE SOURCE: Department of Oncology, University of Uppsala, Akademiska sjukhuset, Sweden.
SOURCE: EUROPEAN JOURNAL OF CANCER, (1994) 30A (5) 687-90.
Journal code: 9005373. ISSN: 0959-8049.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941021
Last Updated on STN: 19980206
Entered Medline: 19941013

AB Paclitaxel (Taxol) is a new cytotoxic agent with considerable activity in phase II studies on metastatic breast cancer. Paclitaxel for clinical use is dissolved in the solvents **cremophor EL** and ethanol. In this study, we added paclitaxel, formulated either in **cremophor EL** and ethanol or only in ethanol, in increasing concentrations to two parental human breast cancer cell lines (ZR 75-1 and HS 578T) and their corresponding sublines with acquired doxorubicin resistance and P-glycoprotein expression. Paclitaxel dissolved either in ethanol or ethanol plus **cremophor EL**, resulted in steep and almost identical dose-response curves for the parental lines ZR 75-1 and HS 578T, respectively, independent of the solvent used. When paclitaxel was formulated only in ethanol the effects on the corresponding doxorubicin-resistant sublines were significantly reduced compared with paclitaxel dissolved in ethanol plus **cremophor EL**. These effects by **cremophor EL** may partly explain some of the antitumoral effects observed by paclitaxel in anthracycline failing patients.

L132 ANSWER 10 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENTDUPLICATE 1
ACCESSION NUMBER: 2003-13594 DRUGU P G
TITLE: A lipophilic paclitaxel derivative incorporated in a lipid emulsion for parenteral administration.
AUTHOR: Lundberg B B; Risovic V; Ramaswamy M; Wasan K M
CORPORATE SOURCE: Univ.Abo; Univ.British-Columbia
LOCATION: Abo, Fin.; Vancouver, B.C., Can.
SOURCE: J.Controlled Release (86, No. 1, 93-100, 2003) 5 Fig. 22 Ref.
CODEN: JCREEC ISSN: 0168-3659
AVAIL. OF DOC.: Department of Biochemistry and Pharmacy, abo Akademi University, BioCity, P.O. Box 66, 20520 Abo, Finland. (e-mail: bolundbe@abo.fi).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The pharmacological prospects and the pharmacokinetic behavior of i.v. lipophilic paclitaxel (PA, Alexis) derivative, paclitaxel-oleate (PE), incorporated in a nano-size sterically **stabilized** oil-in-water lipid emulsion were studied in female rabbit (in vivo), and in human plasma and human cervical cancer cell line, HeLa (in vitro). Chemicals included in the preparation were egg phosphatidylcholine (lecithin), triolein, dipalmitoyl phosphatidyl ethanolamine, polyoxyethylenesorbitan monooleate (polysorbate-80), oleoyl chloride, carbonyldiimidazole (all Sigma-Chem.) and PEG-phosphatidylethanolamine. PE was cytotoxic against HeLa cells. I.v. 3H-PE in lipid emulsion had greater AUC, higher Cmax and lower systemic clearance than 3H-PA in **cremophor** -EL:ethylalcohol. It conclusion, sterically **stabilized** nano-size lipid emulsion can serve as drug-carrier for PE.

L132 ANSWER 11 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-33410 DRUGU G
TITLE: Manufacture and analysis of a paclitaxel concentrate for a solution for infusion in the hospital pharmacy.
AUTHOR: Theuer H; Scherbel G; Wilken A; Wendt J
LOCATION: Nuremberg; Waldbronn, Ger.
SOURCE: Krankenhauspharmazie (23, No. 3, 93-9, 2002) 8 Fig. 27 Ref.
CODEN: KRANDZ ISSN: 0173-7597
AVAIL. OF DOC.: Apotheke Klinikum Nuernberg Sued, Breslauer Strasse 201, 90471 Nuernberg, Germany. (e-mail: theuer@klinikum-nuernberg.de).
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB A paclitaxel (PX) infusion solution concentrate CS was manufactured using PX, **Cremophor** EL and anhydrous ethanol, and **stabilized** by deep-freezing it to temperatures below 20 deg. The long-term **stability** of this solution when **stored** in a frozen state protected from light was monitored over 12 wk and with only minor decomposition of the solution. The quality characteristics of the PX concentrate in terms of content and chromatographic purity corresponded to those of the proprietary medicinal product from the pharmaceutical industry. **Stabilization** of the solution by freezing thus appears an alternative to the **stabilization** methods described in the literature for PX concentrates, avoids patent infringement and enables hospital pharmacists to manufacture in-house a cheaper product of comparable quality to industrial preparations.

L132 ANSWER 12 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-46398 DRUGU P T S G
TITLE: Tumor targeting by conjugation of DHA to paclitaxel.
AUTHOR: Bradley M O; Swindell C S; Anthony F H; Witman P A; Devanesan P; Webb N L; Baker S D; Wolff A C; Donehower R C
CORPORATE SOURCE: Protarga; The-John-Hopkins-Oncol.Cent.
LOCATION: King of Prussia, Pa.; Baltimore, Md., USA
SOURCE: J.Controlled Release (74, No. 1-3, 233-36, 2001) 2 Fig. 9 Ref.
CODEN: JCREEC ISSN: 0168-3659
AVAIL. OF DOC.: Protarga Inc., 2200 Renaissance Blvd., Suite 450, King of Prussia, PA 19406, U.S.A. (e-mail: mbrad124@aol.com).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Tumor targeting, with concomitant long tumor exposure times, should increase the proportion of cells that move into cycle when the drug concentration is high, which should result in more tumor cell killing. To test this hypothesis, docosahexaenoic **acid** (DHA) was conjugated through an ester bond to the paclitaxel (PAC) 2'-oxygen. The resulting fatty **acid** conjugate (DHA-PAC) does not assemble microtubules and is non-toxic. The antitumor activity and pharmacokinetics of i.v. DHA-PAC were compared with those of free PAC (Taxol; Bristol-Squibb) in tumor-bearing mice. In addition, a phase I clinical study was conducted at The Johns Hopkins Hospital to evaluate the safety of DHA-PAC in patients with solid tumors. The primary side-effect was neutropenia. (conference paper: International Symposium on Tumor Targeted Delivery Systems, Bethesda, Maryland, USA, 2000).

L132 ANSWER 13 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1998-29318 DRUGU G
TITLE: Compatibility of paclitaxel in 5% glucose and 0.9% sodium chloride injections with EVA minibags.
AUTHOR: Xu Q A; Trissel L A; Davis M R
CORPORATE SOURCE: Univ.Texas-A+M-Syst.; Baxter-Healthcare
LOCATION: Houston, Tex., USA; Sydney, Austr.
SOURCE: Aust.J.Hosp.Pharm. (28, No. 3, 156-59, 1998) 2 Fig. 2 Tab. 5 Ref.
CODEN: AUHPAI ISSN: 0310-6810
AVAIL. OF DOC.: The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, U.S.A. (L.A.T.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Paclitaxel (PC, Anzatax, Faulding), formulated in **cremophor**-EL and ethyl-alcohol, was chemically **stable** at 0.3 and 1.2 mg/ml in 5% glucose injection and in 0.9% NaCl (both Am.Mcgaw) injection

solutions in ethylene-vinyl-acetate polymer (EVA, Baxter-Healthcare) minibags for up to 72 hr at 25 and 32 deg. Some material of unknown identity, but which was possibly polymer of varying associated acetate groups, was leached into the drug admixture from the container within 24 hr.

L132 ANSWER 14 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-13105 DRUGU P G S
TITLE: Liposomal delivery system for taxol.
AUTHOR: Shieh M F; Chu I M; Lee C J; Kan P; Hau D M; Shieh J J
CORPORATE SOURCE: Univ.Nat.Tsing-Hua
LOCATION: Hsinchu, Taiwan
SOURCE: J.Ferment.Bioeng. (83, No. 1, 87-90, 1997) 4 Fig. 2 Tab. 16 Ref.
CODEN: JFBIEX ISSN: 0922-338X
AVAIL. OF DOC.: Department of Chemical Engineering, National Tsing Hua University, Hsinchu, Taiwan 300, R.O.C.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Liposomal i.p. administration of taxol (Yunnan) was better than with ethanol:**Cremophor** EL, achieving greater **stability** and therapeutic effects in tumor-bearing mice, and fewer side-effects. A 7:3 ratio of egg phosphatidylcholine: dimyristoylphosphatidylglycerol (EPC:DMPG) with 40% cholesterol, 25% alpha-tocopherol (all Sigma-Chem.) and 3% taxol was the best formulation. **Storage** at 4 deg achieved the best **stability**. Mouse mortality and mean survival time were improved in the liposomal groups, and higher doses were tolerated. Mouse activity was greater in the liposomal group, compared to mice given the ethanol/**Cremophor** EL who were dazed and motionless.

L132 ANSWER 15 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-15739 DRUGU G
TITLE: The extraction of diethylhexylphthalate (DEHP) from polyvinyl chloride components of intravenous infusion containers and administration sets by paclitaxel injection.
AUTHOR: Allwood M C; Martin H
CORPORATE SOURCE: Univ.Derby
LOCATION: Derby, U.K.
SOURCE: Int.J.Pharm. (127, No. 1, 65-71, 1996) 2 Fig. 2 Tab. 12 Ref.
CODEN: IJPHDE ISSN: 0378-5173
AVAIL. OF DOC.: Medicines Research Unit, University of Derby, Mickleover, Derby DE3 5GX, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Paclitaxel (PT, Taxol) injection contains **cremophor** and ethanol, agents known to leach diethylhexylphthalate (DEHP) from PVC infusion bags and administration sets. The extent of DEHP extraction by PT injection contained in PVC i.v. infusion bags and given by either PVC or non-PVC sets was studied. During infusion, increasing amounts of DEHP were leached into the PT vehicle from PVC infusion bags and standard PVC sets. DEHP extracted was dependent on the concentration of the PT vehicle, the length of contact between injection vehicle and container and the type of administration set. DEHP level was at its lowest when a non-PVC set was used. The addition of PT to the infusate, administered by non-PVC sets, led to no increase in DEHP extraction. There is only minimal risk of DEHP exposure from PT infusion contained in PVC bags and given through non-PVC administration sets.

L132 ANSWER 16 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-19689 DRUGU G
TITLE: Parenteral formulations for the administration of paclitaxel.
AUTHOR: Simamora P; Dannenfelser R M; Tabibi S E; Yalkowsky S H
CORPORATE SOURCE: Univ.Arizona; Nat.Cancer-Inst.Bethesda
LOCATION: Tucson, Ariz.; Bethesda, Med., USA
SOURCE: Pharm.Res. (12, No. 9, Suppl., S-232, 1995)
CODEN: PHREEB ISSN: 0724-8741
AVAIL. OF DOC.: Department of Pharmaceutical Sciences, University of Arizona, Tucson, AZ 85721, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Paclitaxel is a natural product active against a number of human cancers. It is very insoluble in water and contains no groups that are ionizable in an acceptable pH range. It has a very low solubility in most cosolvents. The current FDA-approved paclitaxel formulation for i.v. administration contains an equal amount of **Cremophor** EL and ethanol. The former is notorious for producing allergic reactions. 2 Potential parenteral formulations containing 5 mg/ml and 3.5 mg/ml of taxol for i.v. administration that are **cremophor**-free and do not precipitate upon dilution have been developed. Both formulations were chemically and physically **stable** for at least 3 mth when **stored** at 4 deg. (conference abstract). (No EX).

L132 ANSWER 17 OF 38 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1994-25127 DRUGU T P G
TITLE: Preparation, administration, **stability**, and compatibility with other medications.
AUTHOR: Goldspiel B R
LOCATION: Bethesda, Maryland, United States
SOURCE: Ann.Pharmacother. (28, No. 5, Suppl., S23-S26, 1994) 1 Fig. 1 Tab. 99 Ref.
CODEN: APHRER ISSN: 1060-0280
AVAIL. OF DOC.: Pharmacy Department, Warren G. Magnuson Clinical Center, Bethesda, MD 20892, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Preparation, administration, **stability** and compatibility of paclitaxel is reviewed. Taxol is the only available formulation and is formulated as a concentrated solution containing paclitaxel, **Cremophor** EL, polyoxyethylated **castor oil** and dehydrated alcohol. **Cremophor** EL leaches di(2-ethylhexyl) phthalate (dioctyl-phthalate, DEHP) from PVC i.v. tubings. DEHP is hepatotoxic and carcinogenic in animals. Preliminary studies suggest that triocytl trimellitrate (TOTM) leaches much less and is less hepatotoxic than DEHP. DEHP is not detected after **storage** in glass or polyolefin containers, but was present in large amounts after **storage** in PVC bags. The visual and turbidimetric compatibility of paclitaxel with other drugs is discussed.

L132 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
ACCESSION NUMBER: 2001:545477 CAPLUS
DOCUMENT NUMBER: 135:112075
TITLE: Purifying polyoxyethylated castor oils with activated charcoal and pharmaceutical formulations thereof
INVENTOR(S): Zhang, Kai; Smith, Gregory A.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052838	A1	20010726	WO 2001-US1749	20010119

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1251845	A1	20021030	EP 2001-904925	20010119

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: US 2000-177459P P 20000120
WO 2001-US1749 W 20010119

AB Disclosed are polyoxyethylated castor oils produced by prepg. a suspension of activated charcoal and a polyoxyethylated castor oil; and sepg. the activated charcoal from the polyoxyethylated castor oil. The process removes impurities such as colorants and alkali metal cations. Also disclosed are compns. contg. the treated castor oil and an active agent such as a pharmaceutical agent. The formulations have prolonged **storage stability**.

IT **64-17-5, Ethanol**, processes **77-92-9, Citric acid**, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(purifying polyoxyethylated castor oils with activated charcoal and pharmaceutical formulations)

IT **33069-62-4, Paclitaxel**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(purifying polyoxyethylated castor oils with activated charcoal and pharmaceutical formulations)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 1994:491880 CAPLUS
DOCUMENT NUMBER: 121:91880
TITLE: Injectable **taxol** composition
INVENTOR(S): Elliott, Robyn Louise; Handreck, Gregory Paul; Carver, David; Prout, Timothy; Ewald, Hernita
PATENT ASSIGNEE(S): F.H. Faulding and Co. Ltd., Australia
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9412198	A1	19940609	WO 1993-AU599	19931125

W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,

BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2149150	AA	19940609	CA 1993-2149150	19931118
CA 2308082	AA	19940609	CA 1993-2308082	19931118
EP 674510	A1	19951004	EP 1994-901593	19931118
EP 674510	B1	19980805		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
EP 835657	A1	19980415	EP 1997-121710	19931118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AU 9351967	A1	19940609	AU 1993-51967	19931125
AU 667142	B2	19960307		
AU 9455538	A1	19940622	AU 1994-55538	19931125
ZA 9308844	A	19940802	ZA 1993-8844	19931126
CN 1096673	A	19941228	CN 1993-115293	19931126
CN 1095266	A	19941123	CN 1993-120529	19931127
CN 1047305	B	19991215		
US 6306894	B1	20011023	US 2000-563969	20000503
US 2003065022	A1	20030403	US 2001-970558	20011004

PRIORITY APPLN. INFO.:

AU 1992-6074	A	19921127
US 1992-995501	A	19921222
CA 1993-2149150	A3	19931118
EP 1994-901593	A3	19931118
WO 1993-US11209	W	19931118
WO 1993-AU599	W	19931125
US 1996-594478	A3	19960131
US 1997-979836	A1	19971126
US 1999-356158	A1	19990719
US 2000-563969	A1	20000503

AB An injectable soln. of taxol with improved stability has a pH less than 8.1, preferably 1 to 8, more preferably 5 to 7.5. The pH is adjusted by addn. of an acid, preferably citric acid, and the preferred compn. comprises taxol, Cremophor EL, citric acid and ethanol.

IT **33069-62-4, Taxol**
RL: BIOL (Biological study)
(injections contg. ethoxylated castor oil and citrate and, stable)

IT **64-19-7, Acetic acid**, biological studies
77-92-9, Citric acid, biological studies
RL: BIOL (Biological study)
(**taxol** injections contg. ethoxylated castor oils and)

IT **64-17-5, Ethanol**, biological studies
RL: BIOL (Biological study)
(**taxol** injections contg. ethoxylated castor oils and acid and)

L132 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:221488 CAPLUS
DOCUMENT NUMBER: 138:226787
TITLE: Injectable composition of **paclitaxel**
INVENTOR(S): Lee, Woo-Young; Lee, Sang-Heon; Kim, Kye-Hyun
PATENT ASSIGNEE(S): Choongwae Pharma Corporation, S. Korea
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022247	A1	20030320	WO 2002-KR1696	20020909

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: KR 2001-55511 A 20010910

AB The disclosure concerns an injectable compn. of paclitaxel, more particularly, an injectable compn. of paclitaxel having excellent anticancer effect comprising a solubilizer such as polyoxyl hydrogenated castor oil, anhyd. ethanol and stabilizer such as N-acetylamino acid. The injectable compns. of paclitaxel provide an effect higher than that of the known compns. showing not only a lower toxicity but also superior soly. of paclitaxel and stability at room temp., thus enabling venous injection by having fine particles. Paclitaxel (6 mg; 0.6%) was added to the soln. of 527 mg (56.7%) Cremophor EL and 0.5 mL anhyd. EtOH. The mixt. was stirred for 30 min to obtain the injectable compn. of Paclitaxel.

IT **64-17-5**, **Ethanol**, biological studies **77-92-9**, **Citric acid**, biological studies **33069-62-4**, **Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable compn. of **paclitaxel**)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:5758 CAPLUS
DOCUMENT NUMBER: 138:78450
TITLE: Particles with improved solubilization capacity
INVENTOR(S): Anderson, David M.
PATENT ASSIGNEE(S): Lyotropic Therapeutics, Inc, USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000236	A1	20030103	WO 2002-US19623	20020621

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003022242	A1	20030130	US 2002-176112	20020621

PRIORITY APPLN. INFO.: US 2001-300476P P 20010623

AB Structured materials and particles that are suitable for solubilizing poorly sol. and poorly-absorbed compds. at high loadings of active while minimizing the chance of pptn. of the active are described. A particle comprises a first vol. of hydrophobe-rich material with tunable dissoln. and solubilization characteristics and a distinct second vol. of nanostructural non-lamellar liq. cryst. material, the second vol. contg. the first domain and being capable of being in equil. with the first vol. Preferably, the nanostructured non-lamellar liq. cryst. material is capable of being in equil. with a polar solvent, a water-immiscible solvent or both. For example, 0.827 g of sweet basil oil was mixed with

0.765 g of the water-insol. surfactant Tween 85, 0.395 g of .alpha.-tocopherol, and 0.955 g water, and the mixt. was centrifuged for 16 h. At that time a basil oil-rich top phase had sepd. out which was decanted. A Tween-rich middle layer contg. a reversed-type liq. cryst. phase was present as well as a bottom aq. phase. About 4 mL of water was added to the middle and bottom layers and this mixt. sonicated forming a crude dispersion. Estradiol (15 mg) was dissolved in 0.594 g of the basil oil-rich top phase, and the following were overlaid on this soln.: 2.463 g of the crude dispersion, 2.452 g of water, 18 mg of sodium taurocholate and 28 mg of Pluronic F68. The mixt. was then sonicated, yielding microdroplets having an estradiol-contg. basil-rich core, coated by a reversed liq. cryst. material.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of particles with improved solubilization capacity contg. bioactive oil as liq. phase embedded within non-lamellar liq. crystals)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:923642 CAPLUS
DOCUMENT NUMBER: 136:74618
TITLE: Prodrug compounds with isoleucine
INVENTOR(S): Pickford, Lesley B.; Gangwar, Sanjeev; Lobl, Thomas J.; Nieder, Matthew H.; Yarranton, Geoffrey T.
PATENT ASSIGNEE(S): Corixa Corporation, USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001095943	A2	20011220	WO 2001-US18857	20010611
WO 2001095943	A3	20020829		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1294404	A2	20030326	EP 2001-944442	20010611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-211686P P 20000614
WO 2001-US18857 W 20010611

OTHER SOURCE(S): MARPAT 136:74618

AB The compds. of the invention are modified forms of therapeutic agents. A typical prodrug compd. of the invention comprises a therapeutic agent, an oligopeptide having an isoleucine residue, a stabilizing group and, optionally, a linker group. The prodrug is cleavable by an enzyme assocd. with the target cell. Methods of making and using the compds. are also disclosed.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug compds. with isoleucine)

IT **64-19-7, Acetic acid**, uses
RL: MOA (Modifier or additive use); USES (Uses)

(stabilizing agent; prodrug compds. with isoleucine)

L132 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730547 CAPLUS
DOCUMENT NUMBER: 135:293952
TITLE: Uses of metal salts to stabilize taxane-based compositions
INVENTOR(S): Zhang, Kai; Smith, Gregory A.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072300	A1	20011004	WO 2001-US9416	20010323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-191802P P 20000324

AB Disclosed are compns. contg. a taxane, a carrier and a metal salt of an acid. Also disclosed are methods of stabilizing taxane/carrier compns. and reducing degrdn. of taxanes, e.g., during storage. The methods entail including the metal salt in the taxane compn. or pretreating the carrier with the metal salt, optionally in combination with other pretreatments. The presence of Zn, Fe, or Cu gluconates and FeSO4 decreased degrdn. of paclitaxel in formulations pretreated with Cremophor EL.

IT **77-92-9, Citric acid**, biological studies
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metal salts to stabilize taxane-based compns.)

IT **33069-62-4, Paclitaxel**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metal salts to stabilize taxane-based compns.)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730546 CAPLUS
DOCUMENT NUMBER: 135:278040
TITLE: Taxane-based compositions
INVENTOR(S): Zhang, Kai; Smith, Gregory A.; Gutierrez-Roca, Jose C.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072299	A1	20011004	WO 2001-US9382	20010323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-191802P P 20000324

AB Taxane-based compns. and methods of using the same to achieve target blood levels of a taxane in a mammal, e.g., to treat taxane-responsive malignant and non-malignant diseases, are described. Compns. comprise a taxane, a carrier, a co-solubilizer, and a stabilizer in a form suitable for oral administration to a mammal and they exhibit long-term stability and overall palatability. Methods for using taxane-based compns. as anal. tools for pharmacokinetic studies are also disclosed. For example, a soln. was prepd. contg. Paclitaxel 12 mg, vitamin E TPGS 400.00 mg, propylene glycol 400.00 mg, ascorbyl palmitate 5.0 mg, dl-.alpha.-tocopherol 5.0 mg and d Dehydrated alc. to 1.0 mL.

IT **33069-62-4, Paclitaxel**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(bioavailability, palatability, and stability of oral taxane-based compns.)

IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, esters
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bioavailability, palatability, and stability of oral taxane-based compns.)

IT **105454-04-4**, 7-Epitaxol
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(degrdn. product; bioavailability, palatability, and stability of oral taxane-based compns.)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:228688 CAPLUS
DOCUMENT NUMBER: 134:271250
TITLE: Surface modified particulate pharmaceutical compositions containing surfactants
INVENTOR(S): Pace, Gary W.; Mishra, Awadhesh K.; Snow, Robert A.
PATENT ASSIGNEE(S): RTP Pharma Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021154	A2	20010329	WO 2000-US25880	20000921
WO 2001021154	A3	20011025		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1214059 A2 20020619 EP 2000-970467 20000921
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
JP 2003509453 T2 20030311 JP 2001-524580 20000921
PRIORITY APPLN. INFO.: US 1999-154964P P 19990921
WO 2000-US25880 W 20000921

AB This invention disclosure relates to compns. for the delivery of stable surface modified sub-micron and micron sized particles of water-insol. drugs from a non-aq. medium that self-disperses on exposure to an aq. environment. Thus, compns. of cyclosporine that self-disperse into surface-modified micron- or sub-micron-sized particle suspensions contained cyclosporine 50, Epax 451O-TG 150, vitamin E-TPGS 45, Tween 80 405, and EtOH 150 mg.

IT **64-19-7**, **Acetic acid**, biological studies
77-92-9, **Citric acid**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aq. medium contg.; surface modified particulate pharmaceutical compns. contg. surfactants)

IT **64-17-5**, **Ethanol**, biological studies **33069-62-4**
, **Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surface modified particulate pharmaceutical compns. contg. surfactants)

L132 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:31306 CAPLUS
DOCUMENT NUMBER: 134:105846
TITLE: Clear aqueous dispersions of triglycerides and surfactants for delivery of drugs and nutrients
INVENTOR(S): Chen, Feng-Jing; Patel, Mahesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001001960	A1	20010111	WO 2000-US15133	20000602
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6267985	B1	20010731	US 1999-345615	19990630
EP 1194120	A1	20020410	EP 2000-938039	20000602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003503440	T2	20030128	JP 2001-507455	20000602

PRIORITY APPLN. INFO.: US 1999-345615 A 19990630
WO 2000-US15133 W 20000602

AB The present invention relates to drug and nutrient delivery systems, and in particular to pharmaceutical compns. and methods for improved solubilization of triglycerides and improved delivery of therapeutic agents. Compns. of the present invention include a triglyceride and a

carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the triglyceride and surfactants. An optional therapeutic agent can be incorporated into the compn., or can be co-administered with the compn. The invention also provides methods of enhancing triglyceride soly. and methods of treatment with therapeutic agents using these compns. Several formulations were presented of compns. that can be prepd. according to the present invention using a variety of therapeutic agents. Examples of aq. dispersions include: (1) Cremophor RH-40 0.75, Peceol 0.25, corn oil 0.40, and fenofibrate 0.10; (2) Cremophor RH-40 0.57, Crovol M-40 0.43, corn oil 0.40, and Rofecoxib 0.15; (3) Tween 80 0.70, Tween 85 0.35, Miglyol 812 0.30, Paclitaxel 0.10, and PEG 400 0.25; or (4) Kessco PEG 400 MO 0.33, corn oil 0.30, and Terbinafine 0.25 parts, resp.

IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, esters **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clear aq. dispersions of triglyceride and surfactants for delivery of drugs and nutrients)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:911036 CAPLUS
DOCUMENT NUMBER: 134:76383
TITLE: Oral pharmaceutical compositions containing taxanes
INVENTOR(S): Gutierrez-Rocca, Jose C.; Cacace, Janice L.; Selim, Sami; Testman, Robert; Rutledge, J. Michael
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078247	A1	20001228	WO 1999-US13821	19990618
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9946955	A1	20010109	AU 1999-46955	19990618
BR 9917403	A	20020709	BR 1999-17403	19990618
EP 1221908	A1	20020717	EP 1999-930408	19990618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
JP 2003502349	T2	20030121	JP 2001-504316	19990618

PRIORITY APPLN. INFO.: WO 1999-US13821 A 19990618

AB Pharmaceutical compns. for oral administration to mammalian subjects comprise a taxane or taxane deriv. (e.g., paclitaxel or docetaxel) as active ingredient and a vehicle comprising at least 30% by wt. of a carrier for the taxane, the carrier having an HLB value of at least about 10. The compns. may also comprise 0-70% of a viscosity-reducing co-solubilizer. The compns. may be incorporated into conventional oral pharmaceutical dosage forms, or can be in the form of a 2-part drug

wherein the first part includes the taxane in a solubilizing vehicle and the second part comprises a carrier for the taxane to promote oral absorption. Methods of treatment of taxane-responsive disease conditions employing the novel compns. are also disclosed, whereby the compns. can be administered alone or in assocn. with an oral bioavailability enhancing agent. A formulation contg. Tween 80 at 18 mg/kg and paclitaxel gave an abs. bioavailability of 54% which was >15% for i.v. drug.

IT **33069-62-4, Paclitaxel**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(oral pharmaceuticals contg. taxanes)

IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, esters
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceuticals contg. taxanes)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:608551 CAPLUS
DOCUMENT NUMBER: 133:213151
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6294192	B1	20010925	US 1999-258654	19990226
NZ 513810	A	20010928	NZ 2000-513810	20000105
EP 1158959	A1	20011205	EP 2000-901394	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537317	T2	20021105	JP 2000-600619	20000105
US 2002012680	A1	20020131	US 2001-898553	20010702
US 6451339	B2	20020917		

PRIORITY APPLN. INFO.: US 1999-258654 A 19990226
WO 2000-US165 W 20000105

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the surfactants contg. the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical compn. contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium

taurocholate 0.26, and propylene glycol 0.46 mg.
IT **64-17-5, Ethanol**, biological studies **77-92-9D, Citric acid**, diglycerides **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:378166 CAPLUS
DOCUMENT NUMBER: 133:22425
TITLE: Stabilized injectable pharmaceutical compositions containing taxoid antineoplastic agents
INVENTOR(S): Owens, Walter H.; Irby, Timothy
PATENT ASSIGNEE(S): Mylan Pharmaceuticals, Inc., USA
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6071952	A	20000606	US 1998-203350	19981202
US 6153644	A	20001128	US 1999-432084	19991102
WO 2000032186	A2	20000608	WO 1999-US28268	19991201
WO 2000032186	A3	20001116		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1135120	A2	20010926	EP 1999-964007	19991201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-203350 A3 19981202
WO 1999-US28268 W 19991201

AB The long term **storage stability** of injectable pharmaceutical compns. comprising a taxane or taxoid is improved by incorporating an effective amt. of an antioxidant. In an injectable container, 1.8 g of paclitaxel were mixed with 150 mL of dehydrated alc., 150 mL of polyethylene glycol 400, and 50.0 mL of an aq. 0.05% thiophenol soln. and stirred vigorously to assure complete soln. To the soln. was added sodium metabisulfite and Cremophor EL-P to make 0.01% and 50% in the soln. The soln. was stored for 5 h ate 105.degree.. Antioxidant stabilized formulation yielded an impurity profile with a lower overall total impurities content as compared with the controls.
IT **33069-62-4, Paclitaxel**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized injectable pharmaceutical compns. contg. taxoid antineoplastic agents)
IT **105454-04-4**, 7-epi-**Taxol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized injectable pharmaceutical compns. contg. taxoid antineoplastic agents)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:640689 CAPLUS
DOCUMENT NUMBER: 131:262644
TITLE: Anticancer **storage stable** self-emulsifying preconcentrate compositions
INVENTOR(S): Parikh, Indu; Moussa, Iskandar; Carrier, Alain
PATENT ASSIGNEE(S): Rtp Pharma Inc., USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9949848	A1	19991007	WO 1999-US7162	19990330
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326485	AA	19991007	CA 1999-2326485	19990330
AU 9933770	A1	19991018	AU 1999-33770	19990330
EP 1067908	A1	20010117	EP 1999-915190	19990330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002509877	T2	20020402	JP 2000-540814	19990330
SE 2000003449	A	20001123	SE 2000-3449	20000927

PRIORITY APPLN. INFO.:
US 1998-80272P P 19980401
US 1998-80273P P 19980401
WO 1999-US7162 W 19990330

AB Pharmaceutical dosage forms for anticancer drugs, and paclitaxel in particular, are described in which the active drug is formulated as **storage stable** self-emulsifying preconc. A compn. contained Miglyol 840 1.971, Cremophor RH40 2.190, Imwitor 308 0.767, Labrasol 0.548, and paclitaxel 0.175 g.

IT **64-17-5, Ethanol**, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer **storage stable** self-emulsifying preconc. compns.)

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer **storage stable** self-emulsifying preconc. compns.)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:220012 CAPLUS
DOCUMENT NUMBER: 130:242336
TITLE: Pharmaceuticals in parenteral formulations containing plasma protein
INVENTOR(S): Hegedus, Lajos; Krempels, Krisztina; Paal, Krisztina; Petho, Gabor

Searched by Barb O'Bryen, STIC 308-4291

PATENT ASSIGNEE(S): Human Rt., Hung.
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913914	A1	19990325	WO 1998-HU86	19980917
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893623	A1	19990405	AU 1998-93623	19980917
AU 734695	B2	20010621		
EP 981375	A1	20000301	EP 1998-946629	19980917
EP 981375	B1	20030108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001508806	T2	20010703	JP 1999-517576	19980917
NZ 503302	A	20010831	NZ 1998-503302	19980917
BR 9812469	A	20020205	BR 1998-12469	19980917
AT 230611	E	20030115	AT 1998-946629	19980917
ZA 9808585	A	20000313	ZA 1998-8585	19980918
LV 12493	B	20010120	LV 2000-38	20000314
NO 2000001371	A	20000518	NO 2000-1371	20000316
LT 4736	B	20001227	LT 2000-18	20000317

PRIORITY APPLN. INFO.: HU 1997-1554 A 19970918
WO 1998-HU86 W 19980917

OTHER SOURCE(S): MARPAT 130:242336

AB The invention is related to water-sol. products and pharmaceutical formulations in solid or liq. form mainly for parenteral use. They consist of or comprise a therapeutically active substance (having low aq. soly. and a substantial binding affinity to plasma proteins) and a plasma protein fraction in controlled aggregation state, whereby the said active substance and the said protein fraction are bound to each other by way of noncovalent bonds. It also covers processes for the prepn. of the product and pharmaceutical formulation.

IT **64-17-5**, **Ethanol**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(pharmaceuticals in parenteral compns. contg. plasma protein)

IT **33069-62-4**, **Paclitaxel**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceuticals in parenteral compns. contg. plasma protein)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:655956 CAPLUS
DOCUMENT NUMBER: 131:291282
TITLE: Nonaqueous compositions for parenteral administration comprising a saccharide fatty acid ester
INVENTOR(S): Johnson, David Farley; Quinlan, James M.
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5965603	A	19991012	US 1998-111951	19980708
BR 9802492	A	20000118	BR 1998-2492	19980720

PRIORITY APPLN. INFO.: US 1997-53234P P 19970721
CA 1997-2211949 A 19970729

AB Nonaq. compns. comprising a saccharide fatty acid ester and an active compd. is provided. The nonaq. compns. of this invention may be parenterally administered to animals and humans. In particular, the nonaq. compns. of the present invention are useful for preventing, controlling or treating helminth, acarid or arthropod endo- or ectoparasitic infection or infestation in warm-blooded animals. A non aq. compn. contained moxidectin 1.05, sucrose monolaurate 10.00, ethanol 20.00, and propylene glycol 67.85%. The compn. remained as a **stable** clear soln. after 18 mo **storage** at 30.degree.. Serum level of moxidectin in cattles treated with the compn. was studied.

IT **33069-62-4, Paclitaxel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonaq. compns. for parenteral administration comprising saccharide fatty acid ester)

IT **64-17-5, Ethanol**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(nonaq. compns. for parenteral administration comprising saccharide fatty acid ester)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:589441 CAPLUS
DOCUMENT NUMBER: 131:276889
TITLE: Pharmacopeia versus practice: extraction of di(2-ethylhexyl) phthalate from PVC by the solvents of **paclitaxel**, docetaxel, and etoposide
AUTHOR(S): Kalmeijer, M. D.; Lauwen, J.; Stuurman, A.
CORPORATE SOURCE: Neth.
SOURCE: Pharmaceutisch Weekblad (1999), 134(33), 1143-1149
CODEN: PHWEAW; ISSN: 0031-6911
PUBLISHER: Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie
DOCUMENT TYPE: Journal
LANGUAGE: Dutch

AB Extn. of di(2-ethylhexyl) phthalate (DEHP) from PVC by the solvents of paclitaxel, docetaxel, and etoposide was studied. These solvents were: (a) for paclitaxel: abs. alc. 39.6 g, Cremophor EL to 100 mL; (b) for docetaxel: abs. alc. 13.0, distd. H2O 87.0 g; to 75 mL of this mixt. was added 25 mL polysorbate 80; (c) for etoposide: citric acid monohydrate 209, PhCH2OH 3.0, polysorbate 80 8.0, PEG-300 65.0 g, and abs. alc. to 100 mL. Two methods of extn. were compared: (1) extn. according to the procedure used in the European Pharmacopeia to test PVC containers for blood and blood components for DEHP release (1 h at 37.degree.); (2) extn. at room temp. during the period the prepd. soln. is allowed to be kept according to the product information. The 3 solvents were tested by both methods in 3 different concns. corresponding to body surfaces of 1.5, 2, and 2.5 m2. All samples were analyzed by HPLC. The use of paclitaxel and etoposide solvents resulted in a .apprx.6-fold higher concns. of DEHP with method 2 than with method 1. For the docetaxel solvent, the DEHP concns. found with both methods were comparable. Evidently the method of the

European Pharmacopeia is not suitable for predicting DEHP extn. in practice. The extd. quantities of DEHP with method 2 were .apprx.3.5-fold higher with the etoposide solvent than with the docetaxel solvent. Both still complied with European Pharmacopeia requirements, though administration of docetaxel in PVC is not allowed in the United States. With the paclitaxel solvent, DEHP release exceeded twice the Pharmacopeia limit.

IT **33069-62-4, Paclitaxel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(infusion; pharmacopeia vs. practice: extn. of di(ethylhexyl) phthalate from PVC by solvents of **paclitaxel**, docetaxel, and etoposide)

IT **77-92-9**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent contg.; pharmacopeia vs. practice: extn. of di(ethylhexyl) phthalate from PVC by solvents of **paclitaxel**, docetaxel, and etoposide)

IT **64-17-5, Ethanol**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent; pharmacopeia vs. practice: extn. of di(ethylhexyl) phthalate from PVC by solvents of **paclitaxel**, docetaxel, and etoposide)

L132 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:503255 CAPLUS
DOCUMENT NUMBER: 127:113384
TITLE: Pharmaceutical injection containing taxane with improved solubility and toxicity properties
INVENTOR(S): Almassian, Bijan; Choy, William
PATENT ASSIGNEE(S): Genelabs Technologies, Inc., USA; Almassian, Bijan; Choy, William
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9723208	A1	19970703	WO 1996-US20187	19961219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2240595	AA	19970703	CA 1996-2240595	19961219
AU 9712949	A1	19970717	AU 1997-12949	19961219
AU 724842	B2	20000928		
EP 876145	A1	19981111	EP 1996-943805	19961219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1209059	A	19990224	CN 1996-199939	19961219

PRIORITY APPLN. INFO.: US 1995-576204 A2 19951221
WO 1996-US20187 W 19961219

AB The title injection is claimed. The injection soln. comprises a taxane, such as taxol or docataxel, in a pharmaceutically pure form, a polyoxyethylene sorbitan fatty acid monoester, polyethoxylated castor oil, and ethanol. The polysorbitan and polyethoxylated castor oil are present in amts. effective to reduce the toxicity of the taxane relative to the

toxicity obsd. when either the polysorbitan or polyethoxylated castor oil is used in the absence of the other. An injection soln. contained PEG-300 20, ethanol 10, Cremophor EL 15, Tween 80 5 mL, taxol (I) 300, and anhyd. citric acid 100 mg. The amt. of I in the soln. after 12 wk storage at 37.degree. was 98.7%.

IT **64-17-5, Ethanol.**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(pharmaceutical injection contg. taxane with improved soly. and toxicity properties)

IT **77-92-9, Citric acid**, biological studies
33069-62-4, Taxol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical injection contg. taxane with improved soly. and toxicity properties)

L132 ANSWER 35 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002446622 EMBASE
TITLE: Dosing sequence-dependent pharmacokinetic interaction of oxaliplatin with paclitaxel in the rat.
AUTHOR: Liu J.; Kraut E.H.; Balcerzak S.; Grever M.; D'Ambrosio S.; Chan K.K.
CORPORATE SOURCE: K.K. Chan, College of Pharmacy, Ohio State University, Columbus, OH 43210, United States. chan.56@osu.edu
SOURCE: Cancer Chemotherapy and Pharmacology, (2002) 50/6 (445-453).
Refs: 26
ISSN: 0344-5704 CODEN: CCPHDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: In a phase I clinical trial of oxaliplatin (OPT) in combination with paclitaxel (PXL), a pharmacokinetic interaction was observed when OPT was given as a 2-h i.v. infusion followed by a 1-h i.v. infusion of PXL. The purpose of this study was to use a rat model to evaluate whether the pharmacokinetic interaction between OPT and PXL is dosing sequence-dependent. Methods: One group of rats was given OPT as a 2-h i.v. infusion followed by a 1-h i.v. infusion of PXL formulated in 50% Cremophor EL (CrEL)/50% ethanol (OPT.fwdarw.fPXL), similar to the current phase I clinical protocol. In a second group of rats, the fPXL was infused first to reach a quasi-steady-state plasma level of PXL, followed by an i.v. bolus dose of OPT (CIfPXL.fwdarw.OPT). In a third group of rats, fPXL was replaced with the formulation vehicle, CrEL, which was infused in the same manner as in the second group. Each combination was accompanied with a control of either OPT alone or with replacement of PXL with dextrose 5% in water (CID5W.fwdarw.OPT). The total platinum (Pt) levels in plasma and plasma ultrafiltrate were measured by a validated inductively coupled plasma mass spectrometry (ICPMS) method. The protein binding, red blood cell (RBC) uptake and urinary elimination of Pt were also examined in each group of rats. Results: The concentration-time profiles of plasma Pt and ultrafiltrable Pt followed triexponential decays in all groups of rats. In the rat receiving OPT.fwdarw.fPXL, the terminal elimination rate constant (.gamma.) of plasma Pt increased, with essentially no change in the total body clearance (CL) and the AUC value, when compared to those without PXL infusion (CID5W.fwdarw.OPT). The (steady-state volume of distribution (V(ss)) of the ultrafiltrable Pt also showed an increase in the combination group receiving OPT.fwdarw.fPXL ($P < 0.01$). These results were similar to those from the clinical trial, although the magnitude of change was less. However, in the CIfPXL.fwdarw.OPT group, both CL and V(ss) of Pt in plasma and plasma ultrafiltrate decreased, with corresponding increases

in AUCs (P < 0.01). The 24-h urinary elimination of total Pt increased in both combination groups, irrespective of the dosing sequence. No difference in protein binding of Pt was observed among the groups. There was a decrease in RBC uptake in the presence of steady-state level of fPXL, but the same was not observed in the OPT.fwdarw.fPXL group. Additionally, similar results were observed with OPT in combination with CrEL alone. Conclusions: These results suggest that alterations in the pharmacokinetics of OPT by fPXL are dosing sequence-dependent and mainly caused by the formulation vehicle CrEL. It is suggested that the dosing sequence of fPXL followed by OPT would be more clinically favorable because it would prolong the residence of OPT in systemic circulation. It is further recommended that the use of other formulations of PXL without CrEL or docetaxel would avoid the complication effect of CrEL.

L132 ANSWER 36 OF 38 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-062579 [08] WPIDS
DOC. NO. CPI: C2001-017625
TITLE: Kit for preparing stable **paclitaxel** formulation for use as anticancer agent, comprising separately stored drug, solution of anhydrous **citric acid** in **ethanol** and solution of polyethoxylated **castor oil** in **ethanol**.
DERWENT CLASS: B02
INVENTOR(S): ORTNER, P
PATENT ASSIGNEE(S): (PBSP-N) PBS PHARM BULK SUBSTANCES SA
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19925211	A1	20001207	(200108)*		3

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19925211	A1	DE 1999-19925211	19990601

PRIORITY APPLN. INFO: DE 1999-19925211 19990601
AB DE 19925211 A UPAB: 20010207
NOVELTY - A kit for preparing a stable **paclitaxel** (I) formulation comprises three sealed sterile vials, respectively containing:
(i) a defined amount of (I);
(ii) a defined solution (A) of anhydrous **citric acid** in **ethanol**; and
(iii) a defined solution (B) of **Cremophor** EL (RTM; polyethoxylated **castor oil**) or **Cremophor** ELP (RTM; polyethoxylated **castor oil**) in **ethanol**
.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(a) a method for preparing a (I) formulation, by dissolving a specific amount of (I) in a specific amount of solution (A), adding a specific amount of solution (B) and shaking the mixture until homogeneous; and
(b) the formulation obtained by method (a).
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - (I) is a cytostatic/cytotoxic agent, useful for treating cancer, e.g. ovarian cancer, breast cancer, lung cancer or leukemia.
ADVANTAGE - Separate storage of the drug, solvent and stabilizer components avoids the stability problems of prior art solution formulations of (I), is less expensive and allows long-term storage.

Concentrated formulations obtained using the kit are chemically, pharmaceutically and microbiologically stable for at least one year. Ready-for-use preparations can be produced rapidly and easily, e.g. by diluting the concentrated formulations with a conventional infusion solution.
Dwg.0/0

L132 ANSWER 37 OF 38 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-571683 [48] WPIDS
DOC. NO. CPI: C1999-166772
TITLE: Taxane composition used for treating e.g. cancer and malaria .
DERWENT CLASS: A23 A25 A96 B02 B04
INVENTOR(S): MCCHESNEY-HARRIS, L L
PATENT ASSIGNEE(S): (NAPR-N) NAPRO BIO THERAPEUTICS INC; (MCCH-I) MCCHESNEY-HARRIS L L
COUNTRY COUNT: 77
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9945918	A1	19990916	(199948)*	EN	45
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AL AU BA BB BG BR CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA UZ VN YU					
ZA 9901885	A	19991027	(199951)		42
AU 9929022	A	19990927	(200006)		
EP 977562	A1	20000209	(200012)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
BR 9904856	A	20000718	(200042)		
CN 1255852	A	20000607	(200046)		
MX 9910340	A1	20000401	(200124)		
KR 2001012363	A	20010215	(200154)		
US 2001029264	A1	20011011	(200162)		
JP 2001524988	W	20011204	(200203)		46

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9945918	A1		WO 1999-US5151	19990310
ZA 9901885	A		ZA 1999-1885	19990309
AU 9929022	A		AU 1999-29022	19990310
EP 977562	A1		EP 1999-909941	19990310
			WO 1999-US5151	19990310
BR 9904856	A		BR 1999-4856	19990310
			WO 1999-US5151	19990310
CN 1255852	A		CN 1999-800022	19990310
MX 9910340	A1		MX 1999-10340	19991110
KR 2001012363	A		KR 1999-710315	19991108
US 2001029264	A1	Provisional	US 1998-77459P	19980310
		Cont of	US 1999-265649	19990310
			US 2001-795626	20010228
JP 2001524988	W		JP 1999-546025	19990310
			WO 1999-US5151	19990310

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9929022	A	Based on	WO 9945918

EP 977562 A1 Based on WO 9945918
BR 9904856 A Based on WO 9945918
JP 2001524988 W Based on WO 9945918

PRIORITY APPLN. INFO: US 1998-77459P 19980310; US 1999-265649 19990310; US 2001-795626 20010228

AB WO 9945918 A UPAB: 19991122
NOVELTY - Composition comprises a taxane and at least one of d- alpha -tocopheryl polyethylene glycol succinate (TPGS), dimethylisosorbide, **citric acid**, methoxy PEG 350, PEG 300 and PEG 4600.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - Used for treating ovarian, prostate or breast cancers, malignant lymphoma, lung cancer, melanoma, Kaposi's sarcoma, polycystic kidney disease, Alzheimer's disease, malaria and rheumatoid arthritis.
ADVANTAGE - The composition has improved stability compared with previous formulations of **paclitaxel**, overcoming its water insolubility and prevents allergic reactions or other side effects. The composition has longer shelf life.
Dwg.0/0

L132 ANSWER 38 OF 38 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-417987 [35] WPIDS
DOC. NO. CPI: C1999-122731
TITLE: Stabilized **paclitaxel** formulations contain e.g. **citric acid**, **ethanol**, a polyglycol ester of 12-hydroxystearic acid and PEG, and an organic solvent e.g. triacetin.
DERWENT CLASS: A28 A96 B02
INVENTOR(S): BURCHETT, M K; CODDINGTON, C A; RAGHAVAN, R; SPEICHER, E R
PATENT ASSIGNEE(S): (ABBO) ABBOTT LAB
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5922754	A	19990713	(199935)*		5
WO 2000020036	A1	20000413	(200026)	EN	
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9958225	A	20000426	(200036)		
EP 1117440	A1	20010725	(200143)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2002526424	W	20020820	(200258)		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5922754	A	US 1998-165930	19981002
WO 2000020036	A1	WO 1999-US21024	19990914
AU 9958225	A	AU 1999-58225	19990914
EP 1117440	A1	EP 1999-945661	19990914
		WO 1999-US21024	19990914
JP 2002526424	W	WO 1999-US21024	19990914
		JP 2000-573394	19990914

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9958225	A	Based on	WO 200020036

EP 1117440 A1 Based on WO 200020036
JP 2002526424 W Based on WO 200020036

PRIORITY APPLN. INFO: US 1998-165930 19981002
AB US 5922754 A UPAB: 19990902
NOVELTY - A composition comprising **paclitaxel**, acid, water, alcohol, a polyglycol ester of 12-hydroxystearic acid and polyethylene glycol, and one or more organic solvents, is new.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - For providing **paclitaxel** formulations which may be terminally sterilized and which show long term stability in water containing mixtures.
ADVANTAGE - **Paclitaxel** compositions can be stabilized without use of **Cremophor** EL(RTM) which has been implicated in causing anaphylactic reactions in some patients. The compositions have extended stability compared to prior art compositions.
Dwg.0/0

=> fil capl; d que 147
FILE 'CAPLUS' ENTERED AT 12:40:55 ON 10 APR 2003
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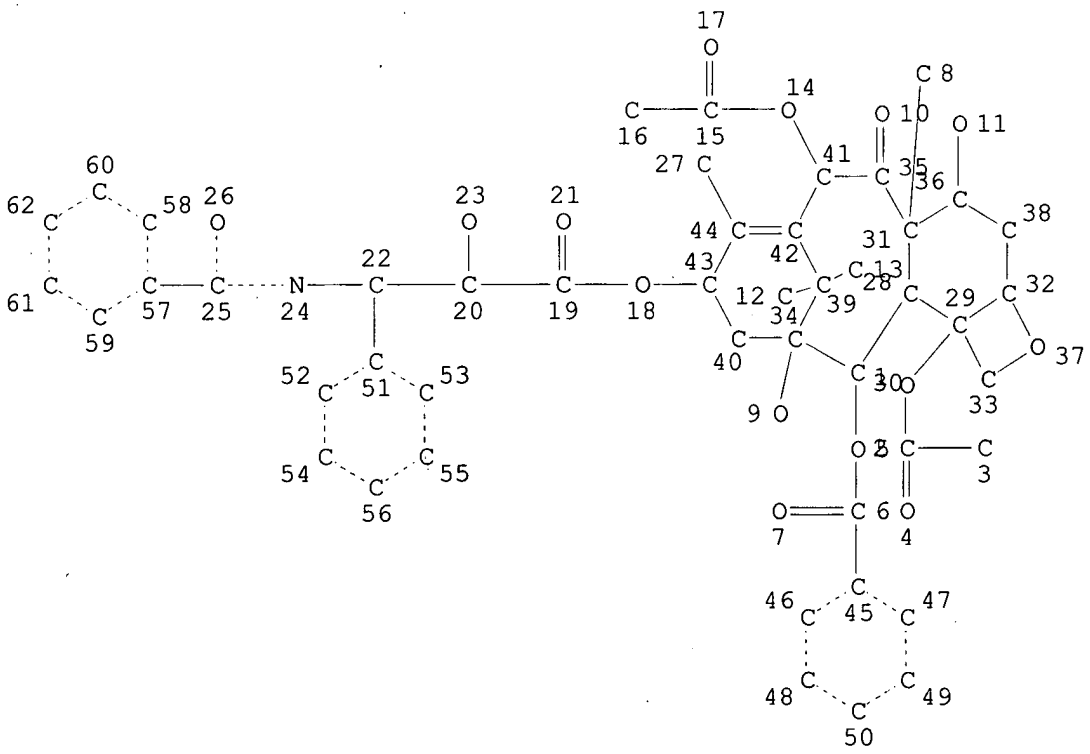
FILE COVERS 1907 - 10 Apr 2003 VOL 138 ISS 15
FILE LAST UPDATED: 9 Apr 2003 (20030409/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L6 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 62

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STEREO ATTRIBUTES: NONE
L8            71 SEA FILE=REGISTRY FAM FUL L6
L13         7488 SEA FILE=CAPLUS ABB=ON  (PACLITAXEL OR TAXOL)/OBI
L14         6976 SEA FILE=CAPLUS ABB=ON  L8
L35       163717 SEA FILE=CAPLUS ABB=ON  SEAL?
L37      2855053 SEA FILE=CAPLUS ABB=ON  ACID#/OBI
L39       417775 SEA FILE=CAPLUS ABB=ON  STOR?
L43       502709 SEA FILE=CAPLUS ABB=ON  CONTAINER# OR VIAL# OR BOTTLE# OR
                 TUBE#
L45       635612 SEA FILE=CAPLUS ABB=ON  CLOS####
L47            5 SEA FILE=CAPLUS ABB=ON  (L13 OR L14) AND (L35 OR L45 OR L39)
                 AND L37 AND L43

=> s l47 not l130
L133           5 L47 NOT L130

=> fil medl; d que l68; d que l69

FILE 'MEDLINE' ENTERED AT 12:40:57 ON 10 APR 2003

  FILE LAST UPDATED: 9 APR 2003 (20030409/UP).  FILE COVERS 1958 TO DATE.

  On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

  MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
  MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/summ2003.html
  for a description on changes.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L57         3004 SEA FILE=MEDLINE ABB=ON  DRUG PACKAGING/CT
L68            6 SEA FILE=MEDLINE ABB=ON  L50 AND L57



L50         7005 SEA FILE=MEDLINE ABB=ON  PACLITAXEL/CT
L55         3038 SEA FILE=MEDLINE ABB=ON  DRUG STORAGE/CT
L56        24342 SEA FILE=MEDLINE ABB=ON  DRUG STABILITY/CT
L69            3 SEA FILE=MEDLINE ABB=ON  L50 AND L56 AND L55

=> s (l68-l69) not l131
L134           9 ((L68 OR L69)) NOT L131

=> fil embase; d que l86; d que l87; d que l89

FILE 'EMBASE' ENTERED AT 12:40:58 ON 10 APR 2003
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  FILE COVERS 1974 TO 3 Apr 2003 (20030403/ED)

  EMBASE has been reloaded. Enter HELP RLOAD for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.
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previously printed

previously printed

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L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L79         1218 SEA FILE=EMBASE ABB=ON  DRUG PACKAGING/CT
L86            2 SEA FILE=EMBASE ABB=ON  L70 AND L79

L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L77         2954 SEA FILE=EMBASE ABB=ON  DRUG STORAGE/CT
L87            3 SEA FILE=EMBASE ABB=ON  L70 AND L77

L70         2358 SEA FILE=EMBASE ABB=ON  PACLITAXEL/CT
L71        76078 SEA FILE=EMBASE ABB=ON  ALCOHOL/CT
L72         6717 SEA FILE=EMBASE ABB=ON  CITRIC ACID/CT
L73        11020 SEA FILE=EMBASE ABB=ON  ACETIC ACID/CT
L74          137 SEA FILE=EMBASE ABB=ON  RICINOMACROGOL/CT
L75          893 SEA FILE=EMBASE ABB=ON  CASTOR OIL/CT
L76          728 SEA FILE=EMBASE ABB=ON  CREMOPHOR/CT
L78        19703 SEA FILE=EMBASE ABB=ON  DRUG STABILITY+NT/CT
L82        81481 SEA FILE=EMBASE ABB=ON  "CARBOXYLIC ACIDS AND THEIR DERIVATIVES
                 "+NT/CT
L89            4 SEA FILE=EMBASE ABB=ON  L70 AND L78 AND ((L71 OR L72 OR L73 OR
                 L74 OR L75 OR L76) OR L82)

=> s (186 or 187 or 189) not 185
L135           8 (L86 OR L87 OR L89) NOT L85

=> fil drugu; d que l109

FILE 'DRUGU' ENTERED AT 12:41:00 ON 10 APR 2003
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FILE LAST UPDATED: 8 APR 2003       <20030408/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<

L90         6155 SEA FILE=DRUGU ABB=ON  PACLITAXEL/CT
L100         802 SEA FILE=DRUGU ABB=ON  PACKAG?
L101         686 SEA FILE=DRUGU ABB=ON  SHELF LIFE
L102         819 SEA FILE=DRUGU ABB=ON  SEAL###
L109           3 SEA FILE=DRUGU ABB=ON  L90 AND (L100 OR L101 OR L102)

=> s l109 not l112
L136           3 L109 NOT L112

=> fil wpids; d que l129; s l129 not l120

FILE 'WPIDS' ENTERED AT 12:41:02 ON 10 APR 2003
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FILE LAST UPDATED:          7 APR 2003      <20030407/UP>
MOST RECENT DERWENT UPDATE:     200323        <200323/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L113        1452 SEA FILE=WPIDS ABB=ON  PACLITAXEL OR TAXOL
L115      813664 SEA FILE=WPIDS ABB=ON  ACID#
L121      906950 SEA FILE=WPIDS ABB=ON  CONTAINER# OR VIAL# OR BOTTLE# OR TUBE#

L122     1137573 SEA FILE=WPIDS ABB=ON  SEAL? OR CLOS####
L123      168528 SEA FILE=WPIDS ABB=ON  PACKAG?
L129           7 SEA FILE=WPIDS ABB=ON  L113 AND L115 AND (L121 OR L123) AND
                 L122

L137           6 L129 NOT L120          previously printed

=> dup rem l134,l136,l133,l135,l137
FILE 'MEDLINE' ENTERED AT 12:41:44 ON 10 APR 2003

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PROCESSING COMPLETED FOR L134
PROCESSING COMPLETED FOR L136
PROCESSING COMPLETED FOR L133
PROCESSING COMPLETED FOR L135
PROCESSING COMPLETED FOR L137
L138          31 DUP REM L134 L136 L133 L135 L137 (0 DUPLICATES REMOVED)
                 ANSWERS '1-9' FROM FILE MEDLINE
                 ANSWERS '10-12' FROM FILE DRUGU
                 ANSWERS '13-17' FROM FILE CAPLUS
                 ANSWERS '18-25' FROM FILE EMBASE
                 ANSWERS '26-31' FROM FILE WPIDS

=> d ibib ab hitrn 1-31; fil hom

L138 ANSWER 1 OF 31     MEDLINE
ACCESSION NUMBER:   1999394835     MEDLINE
```

DOCUMENT NUMBER: 99394835 PubMed ID: 10466923
TITLE: Paclitaxel compatibility with ethylene vinyl acetate bags.
AUTHOR: Goldspiel B R
SOURCE: ANNALS OF PHARMACOTHERAPY, (1999 Jul-Aug) 33 (7-8) 873-4.
Journal code: 9203131. ISSN: 1060-0280.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014

L138 ANSWER 2 OF 31 MEDLINE
ACCESSION NUMBER: 1999356591 MEDLINE
DOCUMENT NUMBER: 99356591 PubMed ID: 10427584
TITLE: Physico-chemical stability of docetaxel premix solution and docetaxel infusion solutions in PVC bags and polyolefine containers.
AUTHOR: Thiesen J; Kramer I
CORPORATE SOURCE: Department of Pharmacy, J. Gutenberg University Hospital, Germany.
SOURCE: PHARMACY WORLD AND SCIENCE, (1999 Jun) 21 (3) 137-41.
Journal code: 9307352. ISSN: 0928-1231.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990920

AB We assessed the physical and chemical stability of docetaxel infusion solutions. Stability of the antineoplastic drug was determined 1.) after reconstitution of the injection concentrate and 2.) after further dilution in two commonly used vehicle-solutions, 0.9% sodium chloride and 5% dextrose, in PVC bags and polyolefine containers. Chemical stability was measured by using a stability-indicating HPLC assay with ultraviolet detection. Physical stability was determined by visual inspection. The stability tests revealed that reconstituted docetaxel solutions (= premix solutions) are physico-chemically stable (at a level > or = 95% docetaxel) for a minimum of four weeks, independent of the storage temperature (refrigerated, room temperature). Diluted infusion solutions (docetaxel concentration 0.3 mg/ml and 0.9 mg/ml), with either vehicle-solution, proved physico-chemically stable (at a level > or = 95% docetaxel) for a minimum of four weeks, when prepared in polyolefine containers and stored at room temperature. However, diluted infusion solutions exhibited limited physical stability in PVC bags, because docetaxel precipitation occurred irregularly, though not before day 5 of storage. In addition, time-dependent DEHP-teaching from PVC infusion bags by docetaxel infusion solutions must be considered.

L138 ANSWER 3 OF 31 MEDLINE
ACCESSION NUMBER: 1999222341 MEDLINE
DOCUMENT NUMBER: 99222341 PubMed ID: 10205627
TITLE: Compatibility of paclitaxel in 5% glucose solution with ECOFLAC low-density polyethylene containers-stability under different storage conditions.
AUTHOR: Sautou-Miranda V; Brigas F; Vanheerswynghels S; Chopineau J
CORPORATE SOURCE: Laboratoire de Pharmacie Clinique et Biotechnique, UFR Pharmacie, Clermont-FD, France.
SOURCE: INTERNATIONAL JOURNAL OF PHARMACEUTICS, (1999 Feb 1) 178

(1) 77-82.
Journal code: 7804127. ISSN: 0378-5173.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990518

AB The compatibility of paclitaxel with low-density polyethylene containers (ECOFLAC) was studied under different temperature and light conditions. Solutions of 0.4 and 1.2 mg/ml of paclitaxel in 5% glucose solution were prepared, put into ECOFLAC containers and stored: (i) at ambient temperature (20-25 degrees C) and in ambient light; (ii) at ambient temperature in the dark; and (iii) at +4 degrees C in the dark. Paclitaxel was assayed by high-performance liquid chromatography after visual inspection of the solutions. The results show that solutions of TAXOL in 5% glucose should not be stored for more than 5 days in glass or ECOFLAC containers because a whitish precipitate tends to form, lowering the paclitaxel concentration. The decrease in the paclitaxel concentration observed after chromatographic analysis ranged very widely (from 12 to 83% of the initial concentration). However solutions of TAXOL diluted in 5% glucose was stable for 5 days in ECOFLAC containers under all the storage conditions tested. These additive-free low-density polyethylene containers offer the advantage of not releasing DEHP into the paclitaxel solutions.

L138 ANSWER 4 OF 31 MEDLINE
ACCESSION NUMBER: 96323928 MEDLINE
DOCUMENT NUMBER: 96323928 PubMed ID: 8739262
TITLE: Plasticizer extraction of Taxol infusion solution from various infusion devices.
AUTHOR: Mass B; Huber C; Kramer I
CORPORATE SOURCE: Apotheke, Klinikum J. Gutenberg Universitat, Mainz, Germany.
SOURCE: PHARMACY WORLD AND SCIENCE, (1996 Apr) 18 (2) 78-82.
Journal code: 9307352. ISSN: 0928-1231.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961022
Last Updated on STN: 19961022
Entered Medline: 19961010

AB Taxol solution extracts the plasticizer DEHP (di(2-ethylhexyl)phthalate) from polyvinyl chloride (PVC) materials. In order to minimize patient exposure to DEHP, Taxol solutions should be prepared and administered in PVC-free materials. Particulate matter may form in Taxol infusion solution over time, so that in-line filtration with microporous membranes not greater than 0.22 microns is advisable. The purpose of this study was to evaluate the suitability of various administration- and in-line filter-sets for Taxol application. The extent of leached DEHP was determined using a Reversed Phase HPLC assay specific for DEHP. The four tested administration-sets, labeled as PVC-free, were all found to be suitable for Taxol application. The tested standard PVC-lined administration-set should not be used for Taxol application. Baxter Intermate LV 250 can be recommended as a disposable infusion device for ambulatory Taxol application. It can be connected with all the tested filter sets.

L138 ANSWER 5 OF 31 MEDLINE
ACCESSION NUMBER: 95160005 MEDLINE

DOCUMENT NUMBER: 95160005 PubMed ID: 7856630
TITLE: Paclitaxel diluent and the case of the slippery spike.
AUTHOR: Martin M; Bepko R
SOURCE: AMERICAN JOURNAL OF HOSPITAL PHARMACY, (1994 Dec 15) 51 (24) 3078, 3080.
Journal code: 0370474. ISSN: 0002-9289.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950316

L138 ANSWER 6 OF 31 MEDLINE
ACCESSION NUMBER: 95023594 MEDLINE
DOCUMENT NUMBER: 95023594 PubMed ID: 7937531
TITLE: Novel taxol formulations: preparation and characterization of taxol-containing liposomes.
AUTHOR: Sharma A; Straubinger R M
CORPORATE SOURCE: Department of Pharmaceutics, University at Buffalo, State University of New York, Amherst 14260-1200.
CONTRACT NUMBER: CA55251 (NCI)
SOURCE: PHARMACEUTICAL RESEARCH, (1994 Jun) 11 (6) 889-96.
Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19980206
Entered Medline: 19941109

AB Taxol is a promising anticancer agent under investigation for therapy of ovarian, breast, colon, and head and neck cancer. One problem associated with the administration of taxol is its low solubility in most pharmaceutically-acceptable solvents; the formulation used clinically contains Cremophor EL (polyethoxylated castor oil) and ethanol as excipients, which cause serious adverse effects. To eliminate this vehicle and possibly improve the antitumor efficacy of taxol, we have formulated taxol in liposomes of various compositions. Liposome formulations containing taxol and phospholipid in the molar ratio 1:33 were prepared from phosphatidylglycerol (PG) and phosphatidylcholine (PC) (1:9 molar ratio), and were physically and chemically stable for more than 2 months at 4 degrees C, or for 1 month at 20 degrees C. A method of producing taxol-liposomes by lyophilization has been developed, by which large batches can be prepared reproducibly in a 'pharmaceutically rational' manner. Taxol-liposomes retained the growth-inhibitory activity of the free drug in vitro against a variety of tumor cell lines. In mice, taxol-liposomes were well-tolerated when given in bolus doses by both iv and ip routes. The Maximum Tolerated Dose (MTD) was > 200 mg/kg; it exceeded that of free taxol, which had a MTD of 30 mg/kg by iv or 50 mg/kg by ip administration. Free taxol administered in the Cremophor vehicle was toxic at doses > 30 mg/kg, as was the equivalent volume of vehicle without drug.(ABSTRACT TRUNCATED AT 250 WORDS)

L138 ANSWER 7 OF 31 MEDLINE
ACCESSION NUMBER: 94218300 MEDLINE
DOCUMENT NUMBER: 94218300 PubMed ID: 7909371
TITLE: A mixed micellar formulation suitable for the parenteral administration of taxol.
AUTHOR: Alkan-Onyuksel H; Ramakrishnan S; Chai H B; Pezzuto J M

CORPORATE SOURCE: Department of Pharmaceutics and Pharmacodynamics, College of Pharmacy, University of Illinois at Chicago 60612.
CONTRACT NUMBER: 2-507-RR 05893-07 (NCRR)
SOURCE: PHARMACEUTICAL RESEARCH, (1994 Feb) 11 (2) 206-12. Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940606
Last Updated on STN: 19970203
Entered Medline: 19940524

AB Taxol is a promising antitumor agent with poor water solubility. Intravenous administration of a current taxol formulation in a non-aqueous vehicle containing Cremophor EL may cause allergic reactions and precipitation upon aqueous dilution. In this study a novel approach to formulate taxol in aqueous medium for i.v. delivery is described. The drug is solubilized in bile salt (BS)/phospholipid (PC) mixed micelles. The solubilization potential of the mixed micelles increased as the total lipid concentration and the molar ratio of PC/BS increased. Precipitation of the drug upon dilution was avoided by the spontaneous formation of drug-loaded liposomes from mixed micelles. The formulation can be stored in a freeze-dried form as mixed micelles to achieve optimum stability, and liposomes can be prepared by simple dilution just before administration. As judged by a panel of cultured cell lines, the cytotoxic activity of taxol was retained when formulated as a mixed-micellar solution. Further, for the same solubilization potential, the mixed-micellar vehicle appeared to be less toxic than the standard nonaqueous vehicle of taxol containing Cremophor EL.

L138 ANSWER 8 OF 31 MEDLINE
ACCESSION NUMBER: 94169491 MEDLINE
DOCUMENT NUMBER: 94169491 PubMed ID: 7907239
TITLE: Paclitaxel stability and compatibility in polyolefin containers.
AUTHOR: Chin A; Ramakrishnan R R; Yoshimura N N; Jeong E W; Nii L J; DiMeglio L S
CORPORATE SOURCE: School of Pharmacy, University of Southern California (USC).
SOURCE: ANNALS OF PHARMACOTHERAPY, (1994 Jan) 28 (1) 35-6. Journal code: 9203131. ISSN: 1060-0280.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19950206
Entered Medline: 19940413

AB OBJECTIVE: To determine the compatibility and stability of paclitaxel in polyolefin containers. DESIGN: The following paclitaxel concentrations were determined by a stability-indicating HPLC method: 0.3 and 1.2 mg/mL diluted in dextrose 5% for injection, USP (D5W) or sodium chloride 0.9% for injection, USP (NS). The solutions were prepared in polyolefin containers and the stability and compatibility were monitored for 48 hours when stored at ambient temperature (20-23 degrees C) and normal fluorescent lighting. A mixture of the drug carrier consisting of approximately 10% polyoxyethylated castor oil (Cremophor EL) and 10% ethanol in D5W and NS, without paclitaxel, was studied to differentiate the effect of paclitaxel from the effect of the drug carrier on the container. Paclitaxel concentrations, pH changes, and visual clarity were used as stability and compatibility indicators. RESULTS: Paclitaxel

concentrations remained at 96-99 percent of the initial concentration for up to 48 hours when placed in the polyolefin containers. No changes in color or visual clarity were noted. Only minor changes in the pH of the admixtures were observed. CONCLUSIONS: Paclitaxel diluted in D5W or NS at concentrations of 0.3 and 1.2 mg/mL is stable and compatible in flexible, polyolefin containers for up to 48 hours.

L138 ANSWER 9 OF 31 MEDLINE
ACCESSION NUMBER: 91353631 MEDLINE
DOCUMENT NUMBER: 91353631 PubMed ID: 1679294
TITLE: Stability, compatibility, and plasticizer extraction of taxol (NSC-125973) injection diluted in infusion solutions and stored in various containers.
AUTHOR: Waugh W N; Trissel L A; Stella V J
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kansas, Lawrence 66045.
CONTRACT NUMBER: NO1-CM-67912 (NCI)
NO1-CM-97576 (NCI)
SOURCE: AMERICAN JOURNAL OF HOSPITAL PHARMACY, (1991 Jul) 48 (7) 1520-4.
Journal code: 0370474. ISSN: 0002-9289.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911020
Last Updated on STN: 19950206
Entered Medline: 19911001

AB The stability of taxol (NSC-125973) in various diluents and containers was determined, and the extent of leaching of di(2-ethylhexyl) phthalate (DEHP) from polyvinyl chloride (PVC) bags caused by the taxol formulation was measured. A taxol formulation consisting of a 6-mg/mL solution of taxol in 50% polyoxyethylated castor oil and 50% dehydrated ethanol was added to 50- and 100-mL glass bottles, PVC infusion bags, and polyolefin containers containing 5% dextrose injection or 0.9% sodium chloride injection to give initial nominal taxol concentrations of 0.3, 0.6, 0.9, and 1.2 mg/mL. The containers were maintained at 20-23 degrees C for 12-24 hours. Samples were assayed by stability-indicating high-performance liquid chromatography, and clarity was determined visually. An experiment was run to ascertain whether DEHP would leach from a PVC administration set during a simulated infusion. There was no substantial loss of taxol over 24 hours. Filtration through a membrane resulted in no loss of taxol. All the solutions initially appeared hazy. Solutions stored in PVC bags became more hazy with time than solutions stored in glass or polyolefin containers. The haze seen in PVC bags was traced to leaching of DEHP. Agitation had no effect on the extent of leaching. Leaching was also seen during simulated delivery through PVC administration sets. No DEHP was detected when solutions were stored in glass or polyolefin containers and infused through polyethylene-lined sets. At the dilutions studied, taxol was visually and chemically stable for up to 24 hours.(ABSTRACT TRUNCATED AT 250 WORDS)

L138 ANSWER 10 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-26328 DRUGU P
TITLE: Nocodazole treatment of CV-1 cells enhances nuclear/perinuclear accumulation of lipid-DNA complexes and increases gene expression.
AUTHOR: Lindberg J; Fernandez M A M; Dezz Ropp J; Hamm Alvarez S F
CORPORATE SOURCE: Univ.Southern-California; Valentis
LOCATION: Los Angeles, Burlingame; Alviso, Cal., USA
SOURCE: Pharm.Res. (18, No. 2, 246-49, 2001) 3 Fig. 1 Tab. 8 Ref.
CODEN: PHREEB ISSN: 0724-8741

AVAIL. OF DOC.: USC School of Pharmacy, 1985 Zonal Avenue, Los Angeles, California 90089-9121, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Nocodazole enhanced the nuclear/perinuclear targeting of lipid-DNA complexes in parallel with increased gene expression of the transfected DNA in CV-1 cells. Nocodazole induced a slight loss of microtubule (MT) polymer during pre-treatment, while taxol increased MT polymer content and accumulation of MT bundles. Nocodazole increased the expression of the luciferase gene encased in either 1-(2-(9-(Z)-octadecenoyloxy))-2-(8)(Z)-heptadecenyl)-3-(hydroxyethyl)imidazolinium chloride (DOTIM):Diphytanoyl phosphoethanolamine (PE) and DOTIM:1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), while taxol had no detectable effect. Results suggest that it is conceivable that the effects of nocodazole on gene targeting and persistence may occur through a MT-independent mechanism.

L138 ANSWER 11 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-36784 DRUGU T S
TITLE: A phase I study of hycamtin following paclitaxel and carboplatin in first line therapy for ovarian cancer.
AUTHOR: Sadozye A; Chan S; Carmichael J
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Obstet.Gynaecol. (106, No. 9, 998-99, 1999)
CODEN: BJOGAS ISSN: 0306-5456
AVAIL. OF DOC.: Queen Elisabeth Hospital, Gateshead, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The standard regimen of paclitaxel 175 mg/sq.m plus carboplatin AUC 6 every 3 wk for 5 cycles followed by 5 cycles of hycamtin (topotecan) 1.25-1.5 mg/sq.m every 3 wk were studied in 30 patients in an open label phase I study. The maximum tolerated dose was reached at 1.5 mg/sq.m for hycamtin. Myelosuppression was the main dose limiting toxicity. In the 1.25 mg/sq.m group 50% of patients had grade III and 16% had grade IV hematological toxicity. In the 1.5 mg/sq.m, 10% patients had grade III and 90% patients had grade IV hematological toxicity. It was concluded that a phase III study should be carried out with the 3 drugs in the above sequence with the dose of hycamtin at 1.25 mg/sq.m (day 1-5). (conference abstract: Spring Scientific Meeting of the British Gynaecological Cancer Society, Liverpool, U.K., 1999). (No EX).

L138 ANSWER 12 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-43391 DRUGU G
TITLE: Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization.
AUTHOR: Loftsson T; Brewster M E
CORPORATE SOURCE: Univ.Iceland
LOCATION: Reykjavik, Iceland
SOURCE: J.Pharm.Sci. (85, No. 10, 1017-25, 1996) 2 Fig. 7 Tab. 108 Ref.
CODEN: JPMSAE ISSN: 0022-3549
AVAIL. OF DOC.: Department of Pharmacy, University of Iceland, P.O. Box 7210, IS-127 Reykjavik, Iceland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Pharmaceutical applications of cyclodextrins (CD) are reviewed. The molecular structure of these glucose derivatives, which approximates a

truncated cone or torus, generates a hydrophilic exterior surface and a nonpolar cavity. CD can interact with appropriately sized molecules leading to the formation of inclusion complexes. These noncovalent complexes offer a variety of physicochemical advantages over the free drugs including enhanced aqueous solubility and solution stability. Chemical modification of the parent CD can lead to enhanced drug complexation and interaction. The stabilizing/destabilizing effects of CD on chemically labile drugs are evaluated.

L138 ANSWER 13 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:564887 CAPLUS
DOCUMENT NUMBER: 135:142255
TITLE: Drug delivery systems for treatment of restenosis and anastomotic intimal hyperplasia
INVENTOR(S): Helmus, Michael N.; Cunanan, Crystal; Tremble, Patrice
PATENT ASSIGNEE(S): Edwards Lifesciences Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001054748	A1	20010802	WO 2001-US2563	20010125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1250166	A1	20021023	EP 2001-905081	20010125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-178087P P 20000125
WO 2001-US2563 W 20010125

AB The invention provides methods for treating injuries to 1 or more internal structures of a subject by administering a drug delivery vehicle to an external surface of the injured structure. The drug delivery vehicle substantially adheres to the site of administration and provides for the release of a bioactive agent that reduces or prevents further injury to the internal structure by disease processes, such as hyperplasia. Thus, a fibrin polymer formulation, polymd. from a mixt. contg. a final concn. of 25-30 mg/mL fibrinogen, 5 IU human factor XIII, 50 IU human thrombin, and paclitaxel was prepd. Also, each **vial** of paclitaxel formulated in delayed-release microspheres was reconstituted with 4 mL sterile saline, and 2 mL of this mixt. was added per **vial** of a **Sealant** Protein Conc. Anal. of the data obtained by angiog. suggested there was no significant difference between control, vehicle and paclitaxel treatment groups.

IT **33069-62-4, Paclitaxel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug delivery systems for treatment of restenosis and anastomotic intimal hyperplasia)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L138 ANSWER 14 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:265217 CAPLUS
DOCUMENT NUMBER: 134:285587
TITLE: Improved methods for delivering bioactive agents using vesicles and ultrasound energy
INVENTOR(S): Unger, Evan C.
PATENT ASSIGNEE(S): ImaRx Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001024705	A1	20010412	WO 2000-US27025	20000929
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001051131	A1	20011213	US 1999-413110	19991006

PRIORITY APPLN. INFO.: US 1999-413110 A 19991006
US 1996-666129 A3 19960619
US 1999-290324 A2 19990412

AB Methods for enhancing the bioavailability of a bioactive agent in vivo are disclosed. Embodiments of the invention involve administering a bioactive agent and an acoustically active compn. to a patient. Ultrasound energy may be applied in an amt. sufficient to activate the acoustically active compn. In preferred form, the acoustically active compn. is administered to the patient at a rate which comprises continuous infusion. To a soln. of saline, propylene glycol, and glycerol (8:1:1) were added dipalmitoyopyosphatidylcholine, dipalmitoylphyosphatidylethanolamine-polyethylene glycol-5000, and dipalmitoylphosphatidic acid in a molar ratio of 82:8:10. The resulting mixt. was heated to about 45.degree. and filtered. The filtered mixt. was placed in a **vial** and allowed to cool to room temp. The **vial** was placed under vacuum to evacuate any gas, after which the **vial** was pressurized with perfluoropropane gas. The **vial** was then **sealed**, placed on a shaker and agitated at room temp. to provide a soln. of perfluoropropane-filled vesicles having a mean diam. of about 2.5 .mu.m. The concn. of vesicles in the soln. was about 1.5x109 vesicle/mL.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improved methods for delivering bioactive agents using vesicles and ultrasound energy)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L138 ANSWER 15 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:906093 CAPLUS
DOCUMENT NUMBER: 136:25134
TITLE: Use of ultrasound for delivering bioactive agents
INVENTOR(S): Unger, Evan C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 38 pp., Cont.-in-part of U. S. Ser. No. 290,324.
CODEN: USXXCO

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001051131	A1	20011213	US 1999-413110	19991006
US 6033645	A	20000307	US 1996-666129	19960619
WO 2001024705	A1	20010412	WO 2000-US27025	20000929

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1996-666129 A3 19960619
US 1999-290324 A2 19990412
US 1999-413110 A 19991006

AB Methods for enhancing the bioavailability of a bioactive agent in vivo is disclosed. Embodiments of the invention involve administering a bioactive agent and an acoustically active compn. to a patient. Ultrasound energy may be applied in an amt. sufficient to activate the acoustically active compn. In preferred form, the acoustically active compn. is administered to the patient at a rate which comprises continuous infusion. To a soln. of saline, propylene glycol and glycerol (8:1:1) were added dipalmitoylphosphatidyl-choline,dipalmitoylphosphatidylethanolamine-PEG5000 and dipalmitolylphosphatidic acid in a molar ratio of 82:8:10. The resulting mixt. was heated to about 45.degree., filtered, and cooled to room temp. The **vial** contg. the mixt. was placed under vacuum to evacuate any gas, after which the **vial** was pressurized with perfluoropropane (PFP). The **vial** was then **sealed**, placed on a shaker and agitated at room temp. to provide a soln. of PFP-filled vesicles having a mean diam. of about 2.5 mm. The soln. of PFP-vesicles was administered i.v. to a healthy human subject at a dose of about 10 mL per Kg of body wt., providing a vesicle dose of about 1.5x107 vesicles/Kg. After injection, a saline flush (5 mL) was administered in the same injection site. Transducers (2.5, 3.5 and 5.0 MHz) were used to image the heart region in both short-axis and long-axis views. After injection of the saline flush, the ultrasound image rapidly darkened until the heart was not visible due to severe shadowing. This severe shadowing lasted for a period of time of about 30 s to about 1 min. Upon dissipation of the shadowing, the ultrasound image revealed only transient contrast enhancement of the myocardial tissues.

IT **33069-62-4, Paclitaxel**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of ultrasound for delivering bioactive agents)

L138 ANSWER 16 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:401630 CAPLUS
DOCUMENT NUMBER: 133:34450
TITLE: Pharmaceutical compositions based on phospholipids and polymers
INVENTOR(S): Leigh, Steven; Leigh, Mathew Louis Steven
PATENT ASSIGNEE(S): Phares Pharmaceutical Research N.V., Neth. Antilles
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000033817	A1	20000615	WO 1999-GB4070	19991208
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
GB 2344520	A1	20000614	GB 1998-27006	19981208
EP 1137402	A1	20011004	EP 1999-961183	19991208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002532389	T2	20021002	JP 2000-586310	19991208

PRIORITY APPLN. INFO.:
GB 1998-27006 A 19981208
GB 1999-25365 A 19991027
WO 1999-GB4070 W 19991208

AB The present invention relates to the prepn. of powder or solid compns. comprising single and double chain amphiphilic lipids in assocn. with polymers which harden them so that they can be comminuted into powder or granules. The compns. can act as carriers for biol. active compds. and can be administered to living organisms. Such a compn. may comprise a biol. active compd. and monoacyl and diacyl membrane lipid in assocn. with a polymer, said compn. being a solid that when **stored** in a glass **container** remains free flowing after 3 mo at 40 >C and 75 % relative humidity. The lipids may be selected from those which have GRAS (generally regarded as safe) status, e.g. enzyme-modified lecithin, and the polymer may be selected from natural polysaccharide polymers, starches and their derivs., cellulose and its derivs. and gelatins. For example, a solid formulation was prepd. contg. flurbiprofen, VP 200 (a lipid contg. 60% by wt. of monoacyl phosphatidylcholine and 40% phosphatidylcholine), and Eudragit in a ratio of 1:10:10, resp. The compn. may be filled into hard gelatin capsules or may be compressed into tablets.

IT **33069-62-4, Taxol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. based on phospholipids and polymers)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L138 ANSWER 17 OF 31 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:865092 CAPLUS
DOCUMENT NUMBER: 134:21486
TITLE: Kit for the production of a formulation of **paclitaxel**
INVENTOR(S): Ortner, Peter
PATENT ASSIGNEE(S): PBS Pharmaceutical Bulk Substances S.A., Switz.
SOURCE: Ger. Offen., 4 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19925211	A1	20001207	DE 1999-19925211	19990601

PRIORITY APPLN. INFO.:
DE 1999-19925211 19990601

AB A kit for the prodn. of a pharmaceutical formulation of paclitaxel, in which the individual components in kept sep. sterile **closed containers**. The formulation is chem. and microbiol. stable. Thus, paclitaxel was mixed with a soln. of citric acid in EtOH (soln. A) and kept in a **vial**. A soln. B consisting of Cremophor EL or Cremophor ELP in EtOH was added to the soln. A. The mixt. was stirred to homogeneity and the conc. obtained can be used for the prepn. of an infusion soln.

IT **33069-62-4, Paclitaxel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kit for prodn. of formulation of **paclitaxel**)

L138 ANSWER 18 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003092701 EMBASE
TITLE: Optimising the therapeutic trinity of active ingredient, delivery system and functional packaging.
AUTHOR: Sam T.
CORPORATE SOURCE: T. Sam, NV Organon, P.O. Box 20, 5340 BH Oss, Netherlands. tom.sam@organon.com
SOURCE: Journal of Controlled Release, (21 Feb 2003) 87/1-3 (153-157).
Refs: 6
ISSN: 0168-3659 CODEN: JCREEC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This paper introduces the "therapeutic trinity" concept for formulating and developing optimal drug products. It starts with the recognition that all drug products are constituted of three distinct elements: the active ingredient, the delivery system and the packaging. Union of these three elements into one trinity will bring therapeutic value to the patient under the condition that active ingredient, delivery system and packaging are developed and optimised interdependently. Optimisation should be performed with the patient in mind, taking into account the relevant efficacy and safety parameters, and the relevant quality and cost parameters. Since the patient plays the central role in the performance of the drug product, biopharmaceutical robustness of and patient compliance towards the active ingredient/delivery system/packaging trinity should be considered important determinants of therapeutic success.

L138 ANSWER 19 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003092295 EMBASE
TITLE: Noncovalent dimerization of paclitaxel in solution: Evidence from electrospray ionization mass spectrometry.
AUTHOR: Lorenz S.A.; Bigwarfe Jr. P.M.; Balasubramanian S.V.; Fetterly G.J.; Straubinger R.M.; Wood T.D.
CORPORATE SOURCE: T.D. Wood, Department of Chemistry, Natural Sciences Complex, State University of New York, Buffalo, NY 14260-3000, United States. twood@acsu.buffalo.edu
SOURCE: Journal of Pharmaceutical Sciences, (1 Sep 2002) 91/9 (2057-2066).
Refs: 40
ISSN: 0022-3549 CODEN: JPMSAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

SUMMARY LANGUAGE: English
AB Paclitaxel, a unique antimitotic chemotherapy agent that inhibits cell division by binding to microtubules and prevents them from "depolymerizing," has received widespread interest because of its efficacy in fighting certain types of cancer, including breast and ovarian cancer. Paclitaxel undergoes aggregation at millimolar concentrations in both aqueous media and solvents of low polarity (mimicking hydrophobic environments). Its aggregation may have impact on its aqueous stability and its ability to stabilize microtubules. Here, we investigated the dimerization phenomenon of paclitaxel by electrospray ionization mass spectrometry (ESI-MS). Paclitaxel dimers were stable in solutions of acetonitrile/aqueous ammonium acetate (80/20) and aqueous sodium acetate/acetonitrile (92/8 or 95/5) at various pH values. Additional experiments using solution-phase hydrogen/deuterium exchange were employed to ascertain whether or not the observed dimers were formed in solution or as an artifact of the ESI process by ion-molecule reaction. The evidence supports formation of the dimer in solution, and the approach used can be extended to investigation of other types of drug-drug interactions. .COPYRGT. 2002 Wiley-Liss, Inc.

L138 ANSWER 20 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002386597 EMBASE
TITLE: Counterfeit cases set stage for Today's Laws, safety mechanisms.
AUTHOR: Fintor L.
SOURCE: Journal of the National Cancer Institute, (2 Oct 2002) 94/19 (1425).
ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
039 Pharmacy
049 Forensic Science Abstracts
LANGUAGE: English

L138 ANSWER 21 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002216109 EMBASE
TITLE: Use of a cholesterol-rich emulsion that binds to low-density lipoprotein receptors as a vehicle for paclitaxel.
AUTHOR: Rodrigues D.G.; Covolan C.C.; Coradi S.T.; Barboza R.; Maranhao R.C.
CORPORATE SOURCE: R.C. Maranhao, Inst. do Coracao Hosp. Clin. FMUSP, Lab. de Metabolismo de Lipides, Av. Dr. Eneas de Carvalho Aguiar, 44, Andar Sao Paulo - SP 05403-000, Brazil. ramarans@usp.br
SOURCE: Journal of Pharmacy and Pharmacology, (2002) 54/6 (765-772).
Refs: 21
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
030 Pharmacology
016 Cancer
029 Clinical Biochemistry
015 Chest Diseases, Thoracic Surgery and Tuberculosis
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A cholesterol-rich emulsion (LDE) is taken up by malignant cells which over-express low-density lipoprotein (LDL) receptors and thus may be used as a carrier for drugs directed against neoplastic cells. In this study,

we associated the antineoplastic agent paclitaxel to LDE and analysed the new formulation's incorporation efficiency, chemical and physical stability, cellular uptake and cytostatic activity against a neoplastic cell line and the acute toxicity to rats. A paclitaxel incorporation efficiency of approximately 75% was achieved when paclitaxel was mixed with LDE at a 6:1 lipid-to-drug molar ratio. The association of paclitaxel with LDE increased by 54% the mean diameter of the emulsion particles but did not damage the paclitaxel chemical structure as analysed by HPLC. Results from gradient ultracentrifugation and Sephadex G25 gel filtration indicated that the binding of the drug to the emulsion was stable. It was shown that the cellular uptake and the cytotoxic activity of LDE-paclitaxel by a neoplastic cell line (NCI-H292 cells) was indeed mediated by the LDL receptors. The anti-proliferative activity of LDE-paclitaxel against NCI-H292 cells was less than that of a commercial paclitaxel preparation (50% inhibitory concentration, IC50 = 2.60 and 0.45 .mu.M, respectively). This difference, however, can be ascribed to the in-vitro anti-proliferative activity of the commercial paclitaxel vehicle Cremophor EL; when Cremophor EL was added to the cultures with LDE-paclitaxel, the IC50 value was reduced to 0.45 .mu.M, attaining that of the commercial paclitaxel preparation. The tolerability of LDE-paclitaxel in rats was remarkable, such that its lethal dose (LD50) was ten-fold greater than that of the commercial formulation (LD50 = 324 and 31.8 mg kg(-1), respectively). Therefore, LDE-paclitaxel association is stable and the cytostatic activity of the drug is preserved while its toxicity to rats is small. By diminishing the side effects and directing paclitaxel to neoplastic tissues, LDE may be useful as adjuvant in chemotherapy with this drug.

L138 ANSWER 22 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003044416 EMBASE
TITLE: HPMA copolymers platinates containing dicarboxylato ligands. Preparation, characterisation and in vitro and in vivo evaluation.
AUTHOR: Gianasi E.; Buckley R.G.; Latigo J.; Wasil M.; Duncan R.
CORPORATE SOURCE: R. Duncan, Centre for Polymer Therapeutics, Welsh School of Pharmacy, King Edward VII Ave, Cardiff CF10 3XF, United Kingdom. duncanr@cf.ac.uk
SOURCE: Journal of Drug Targeting, (2002) 10/7 (549-556).
Refs: 32
ISSN: 1061-186X CODEN: JDTAEH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB N-(2-Hydroxypropyl) methacrylamide (HPMA) copolymer platinates were prepared from polymeric intermediates containing Gly-Phe-Leu-Gly side chains terminating in either malonate or aspartate dicarboxylato ligands. Platinum(II) was bound by reaction of the dicarboxylato ligands with wt% (by AAS). This is close to the theoretical maximum value. The release rate of platinum species in vitro at pH 7.4 correlated with the expected stability of the 6 and 7 membered chelate rings; 14%/24 h platinum released in the case of the malonate and 68%/24 h platinum released in the case of the aspartate. Cisplatin and the aspartate conjugate displayed similar toxicity in vitro against B16F10 and COR-L23 cells while the malonate was at least 8-fold less toxic. The malonate conjugate showed significantly improved activity (T/C = 1.27-1.5) when compared with cisplatin (T/C = 1.18) that was not active when administered intravenously

to treat a subcutaneous B16F10 tumour. The conjugate was at least 20-fold less toxic than cisplatin in vivo. After i.v. administration, the platinum accumulation in B16F10 tumour tissue showed a 19-fold increase in Pt AUC for the malonate conjugate when compared to cisplatin administered equi-dose at its maximum tolerated dose (MTD) (1 mg/kg).

L138 ANSWER 23 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002200255 EMBASE
TITLE: Pilot study of hydrolytically activated paclitaxel prodrug therapy in patients with progressive malignancies.
AUTHOR: Wrasidlo W.; Niethammer A.; Deger S.; Sehouli J.; Kulozik A.; Geilen W.; Henze G.; Gaedicke G.; Lode H.N.
CORPORATE SOURCE: Dr. H.N. Lode, Charite Children's Hospital, Forschungshaus 2.0407, Augustenburgerplatz 1, 13353 Berlin, Germany. holger.lode@charite.de
SOURCE: Current Therapeutic Research - Clinical and Experimental, (2002) 63/4 (247-262).
Refs: 32
ISSN: 0011-393X CODEN: CTCEA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: The development of novel strategies based on chemotherapy with prodrugs is still a challenge for physicians developing effective treatment of malignancies in advanced-stage disease. In this study, we tested the hypothesis that this can be achieved by a prodrug of paclitaxel if the C7 hydroxyl group is blocked by condensation with a solketal chloroformate followed by a ring-opening reaction to the dihydroxyl derivative. Objective: The purpose of this study was to obtain information about toxicity, pharmacokinetic characteristics, and outcomes following paclitaxel prodrug therapy in 10 patients suffering from various progressive end-stage malignancies. Methods: Eligible patients had failed standard therapies and presented with progressive disease, were free of acute infections, had a total white blood cell count >2500 cells/mm(3) and platelet count of >150,000 cells/mm(3), and had received chemo- or radiotherapy in the preceding 8 weeks. Subjects were treated with paclitaxel prodrug (pro Taxol) (100-1200 mg/m(2)) under the compassionate-use Investigational New Drug setting, and toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria (version 2.0). Pharmacokinetic characteristics of paclitaxel prodrug and paclitaxel released from the prodrug were determined by high-performance liquid chromatography. Results: Ten patients with different progressive malignancies were enrolled. Pharmacokinetic monitoring of treated patients demonstrated an increase in the serum half-life (~5-fold, 14.0 hours vs 2.9 hours) and the maximum plasma drug concentration (~50-fold, 110.0 .mu.M vs 2.7 .mu.M) of the paclitaxel prodrug over active paclitaxel, respectively. Furthermore, paclitaxel prodrug was shown to convert to active paclitaxel. The patients tolerated doses of .ltoreq.1200 mg/m(2), with transient liver toxicity starting at 450 mg/m(2). Grade 4 neutropenia was observed in 4 patients and required treatment with granulocyte colony-stimulating factor. Among the 10 enrolled patients, we observed 2 with complete remissions, 3 with partial responses, 1 with stable disease, and 4 with progressive disease. Conclusions: In this study, hydrolytically activated therapy with a paclitaxel prodrug resulted in decreased toxicity in patients based on a slow release of active paclitaxel. Encouraging effects on the course of the disease were observed, albeit in a heterogeneous patient population.

These findings indicate that paclitaxel prodrug may further improve the success rate of chemotherapy with active paclitaxel.

L138 ANSWER 24 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002296695 EMBASE
TITLE: Nanostructured lipid matrices for improved microencapsulation of drugs.
AUTHOR: Muller R.H.; Radtke M.; Wissing S.A.
CORPORATE SOURCE: R.H. Muller, Department of Pharmaceutics, Free University of Berlin, Kelchstr. 31, 12169 Berlin, Germany. mpharma@zedat.fu-berlin.de
SOURCE: International Journal of Pharmaceutics, (21 Aug 2002) 242/1-2 (121-128).
Refs: 35
ISSN: 0378-5173 CODEN: IJPHDE
PUBLISHER IDENT.: S 0378-5173(02)00180-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB At the beginning of the nineties solid lipid nanoparticles (SLN) have been introduced as a novel nanoparticulate delivery system produced from solid lipids. Potential problems associated with SLN such as limited drug loading capacity, adjustment of drug release profile and potential drug expulsion during storage are avoided or minimised by the new generation, the nanostructured lipid carriers (NLC). NLC are produced by mixing solid lipids with spatially incompatible lipids leading to special structures of the lipid matrix, i.e. three types of NLC: (I) the imperfect structured type, (II) the structureless type and (III) the multiple type. A special preparation process-applicable to NLC but also SLN-allows the production of highly concentrated particle dispersions (>30-95%). Potential applications as drug delivery system are described.

L138 ANSWER 25 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002114052 EMBASE
TITLE: [Production and quality of Paclitaxel injection produced in the hospital pharmacy].
HERSTELLUNG UND ANALYTIK EINES IN DER KRANKENHAUSAPOTHEKE HERGESTELLTEN PACLITAXEL-INFUSIONSLOSUNGSKONZENTRATS.
AUTHOR: Theuer H.; Scherbel G.; Wilken A.; Wendt J.
CORPORATE SOURCE: Dr. H. Theuer, Apotheke Klin. Nurnberg Sud, Breslauer Strasse 201, 90471 Nurnberg, Germany. theuer@klinikum-nuernberg.de
SOURCE: Krankenhauspharmazie, (2002) 23/3 (93-99).
Refs: 27
ISSN: 0173-7597 CODEN: KRANDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: German
SUMMARY LANGUAGE: English; German
AB The production of Paclitaxel injection in the hospital pharmacy represents a very interesting possibility to reduce therapy costs at a high quality level. The composition, production, quality control methods and stability testing of paclitaxel injection are described. We monitored the stability of the injection solution at light protected storage at < -20.degree.C over a period of 12 weeks. The decomposition rate of Paclitaxel at this temperature was very low, so that the amount after this time was 98,63 % of the initial value and the product conforms the specification. The

long-term stability study continues. The quality of the Paclitaxel injection produced in the hospital pharmacy was found to be at the same level as the industrial products.

L138 ANSWER 26 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-058317 [05] WPIDS
DOC. NO. CPI: C2003-014825
TITLE: Composition used for micellar drug delivery vehicles used for treating e.g. cancer, comprises micelle-forming biocompatible diblock copolymer, polymer and/or water soluble, biocompatible organic solvent and hydrophobic drug.
DERWENT CLASS: A96 B07
INVENTOR(S): GUAN, D; LIGGINS, R; MURPHY, L
PATENT ASSIGNEE(S): (GUAN-I) GUAN D; (LIGG-I) LIGGINS R; (MURP-I) MURPHY L; (ANGI-N) ANGIOTECH PHARM INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002072150	A2	20020919	(200305)*	EN	67

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

US 2003054036 A1 20030320 (200323)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002072150	A2		WO 2002-CA326	20020313
US 2003054036	A1	Provisional	US 2001-275725P	20010313
		Provisional	US 2001-337935P	20011107
			US 2002-99135	20020313

PRIORITY APPLN. INFO: US 2001-337935P 20011107; US 2001-275725P 20010313; US 2002-99135 20020313

AB WO 200272150 A UPAB: 20030121
NOVELTY - Composition comprises:
(a) a micelle-forming biocompatible diblock copolymer having a hydrophilic block comprising residues of monomer, and a hydrophobic block comprising residues of monomer;
(b) an additive comprising polymer and/or a water soluble, biocompatible, organic solvent, and
(c) a hydrophobic drug.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(a) production of the composition which comprises treating the composition according to a sterilization process comprising sterile filtration, sterilization with ethylene oxide or sterilization with ionic radiation;
(b) forming a drug delivery vehicle which comprises adding water to the composition to form a micelle-containing composition;
(c) forming a composition which comprises combining the diblock copolymer, additive and hydrophobic drug with an additional organic (processing) solvent, and removing the organic (processing) solvent by evaporation or distillation, and

(d) preparation of a composition which comprises dissolving a micelle-forming biocompatible diblock copolymer, precipitating or crystallizing the diblock copolymer from the purification solvent, and separating the diblock copolymer from the purification solvent.

ACTIVITY - Cytostatic; Antibacterial; Antiinflammatory; Neuroprotective; Nootropic; Antipsoriatic; Vasotropic; Cardiant.

MECHANISM OF ACTION - None given in the source material.

USE - Used for micellar drug delivery vehicles useful for treating and preventing inflammatory conditions, neurological disorders, cancer, and benign hyperproliferative diseases, particular arthritis, multiple sclerosis, Alzheimer's disease, psoriasis, stenosis or restenosis, benign hyperplasia, cardiovascular disease, inflammatory bowel disease.

ADVANTAGE - The composition forms micelles at an improved rate, have improved ability to incorporate drugs and/or have improved physical properties e.g. viscosity and/or melting point that render the composition easy to make and/or handle.

Dwg.0/0

L138 ANSWER 27 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-732710 [79] WPIDS
DOC. NO. NON-CPI: N2002-577796
DOC. NO. CPI: C2002-207296
TITLE: Implant used for treating vascular narrowing or occlusion, especially for controlling restenosis contains FK506 in chemically bound or physically fixed form.
DERWENT CLASS: A96 B05 B07 D22 P32
INVENTOR(S): VON OEPEN, R; WNENDT, S; KUTTLER, B; LANG, G
PATENT ASSIGNEE(S): (JOME-N) JOMED GMBH
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002065947	A2	20020829	(200279)*	GE	70
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
DE 10107339	A1	20020905	(200279)		
DE 10127011	A1	20021212	(200281)		
DE 10127330	A1	20021212	(200281)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002065947	A2	WO 2002-EP1707	20020218
DE 10107339	A1	DE 2001-10107339	20010216
DE 10127011	A1	DE 2001-10127011	20010605
DE 10127330	A1	DE 2001-10127330	20010606

PRIORITY APPLN. INFO: DE 2001-10127330 20010606; DE 2001-10107339 20010216; DE 2001-10127011 20010605

AB WO 200265947 A UPAB: 20021209

NOVELTY - Implant (A) contains FK506 in chemically bound (covalent or non-covalent) or physically fixed form and optionally at least one other active agent (II).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) preparation of (A) optionally coated with active agents, and
(b) a stent with a polymeric surface including, in chemically bound (covalent or non-covalent) or physically fixed form, at least one physiologically and/or pharmaceutically active agent.
ACTIVITY - Vasotropic.
MECHANISM OF ACTION - None given in the source material.
USE - (A), particularly stents or stent grafts, are used for treatment and prevention of narrowing or occlusion of coronary or peripheral blood vessels, most especially to prevent restenosis.
ADVANTAGE - The FK506 can be incorporated into stents that have already been sterilized.
Dwg.0/7

L138 ANSWER 28 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-571920 [53] WPIDS
DOC. NO. NON-CPI: N2000-423145
DOC. NO. CPI: C2000-170407
TITLE: Simplified unit-dose **packaging** of medicinal zinc chloride mixtures for the topical treatment of melanoma skin cancer and other skin diseases facilitate zinc chloride treatment and dosage control.
DERWENT CLASS: B05 D22 P32
INVENTOR(S): BROOKS, L S; BROOKS, N A
PATENT ASSIGNEE(S): (BROO-I) BROOKS L S; (BROO-I) BROOKS N A
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000048541	A1	20000824	(200053)*	EN	48
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000029989	A	20000904	(200103)		
US 2002081328	A1	20020627	(200245)		
US 2002150630	A1	20021017	(200270)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000048541	A1		WO 2000-US4033	20000216
AU 2000029989	A		AU 2000-29989	20000216
US 2002081328	A1	Provisional	US 1999-120656P	19990219
			US 2000-505618	20000216
US 2002150630	A1	Provisional	US 1999-120656P	19990219
		CIP of	US 2000-505618	20000216
			US 2002-171326	20020612

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000029989	A	Based on	WO 200048541

PRIORITY APPLN. INFO: US 1999-120656P 19990219; US 2000-505618 20000216; US 2002-171326 20020612
AB WO 200048541 A UPAB: 20001023
NOVELTY - Unit-dose **packaging** of medicinal zinc chloride mixtures for the topical treatment of melanoma skin cancer and other skin

diseases is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for:

(1) transdermal applicators for use in treating skin diseases;

(2) humectantly (sic) **sealed**, multi-layered, flexible, transdermal applicators for use in treating skin diseases; and

(3) methods for removing abnormal skin growths.

ACTIVITY - Cytostatic; anti-melanoma; dermatological.

USE - The unit-dose **packagings** are used for the topical treatment of melanoma skin cancer and other skin diseases (claimed). They are used to treat human melanoma, basal and squamous cell skin cancer and a variety of other skin tumors and skin diseases such as warts. They may also be use to treat tumors including neoplasms and carcinomas of the parotid gland, bone, larynx, mouth, accessory nasal sinuses, lips, breast and anal region, sarcomas, actnic and seborrheic keratoses, keratoacanthoma, hemangiomas, lymphangiomas, nevi, warts and other epithelial growths, to safely treat skin cancer patients infected with the AIDS virus, to provide a bactericidal effect on infected tissues, to stimulate the angiogenesis of granulation tissue that results in rapid spontaneous wound healing and to heal infected necrotic tissue of diabetic gangrene.

ADVANTAGE - The **packagings** are simplified compared with prior art dressings for holding zinc chloride pastes. They facilitate the use of treatments using zinc chloride and allow the physician to easily control the dosage of zinc chloride administered while maintaining the zinc chloride in an environmentally controlled atmosphere.

DESCRIPTION OF DRAWING(S) - Bottom and side perspective of a transdermal applicator illustrating the removal of a peel-away strip.

transdermal applicator 10

backing 18

zinc chloride mixture 22

adhesive substrate 24

peel-away strip. 26

Dwg.7/13

L138 ANSWER 29 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-302469 [25] WPIDS
DOC. NO. CPI: C1999-088639
TITLE: Use of arsenic compounds for treatment of solid tumors and metastatic neoplastic disease.
DERWENT CLASS: B05 B06
INVENTOR(S): ELLISON, R M; MERMELSTEIN, F H; ELLISON, R
PATENT ASSIGNEE(S): (POLA-N) POLARX BIOPHARMACEUTICALS INC; (ELLI-I) ELLISON R M; (MERM-I) MERMELSTEIN F H
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9918798	A1	19990422	(199925)*	EN	58
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9910893	A	19990503	(199937)		
EP 1022951	A1	20000802	(200038)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
NO 2000001977	A	20000613	(200040)		
BR 9813085	A	20000822	(200050)		
CN 1282218	A	20010131	(200131)		
KR 2001015755	A	20010226	(200156)		
NZ 503973	A	20010928	(200161)		

JP 2001519366 W 20011023 (200202) 52
MX 2000003653 A1 20010701 (200236)
AU 751932 B 20020829 (200264)
US 2002183385 A1 20021205 (200301)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9918798	A1		WO 1998-US21782	19981015
AU 9910893	A		AU 1999-10893	19981015
EP 1022951	A1		EP 1998-953552	19981015
			WO 1998-US21782	19981015
NO 2000001977	A		WO 1998-US21782	19981015
			NO 2000-1977	20000414
BR 9813085	A		BR 1998-13085	19981015
			WO 1998-US21782	19981015
CN 1282218	A		CN 1998-812218	19981015
KR 2001015755	A		KR 2000-703973	20000414
NZ 503973	A		NZ 1998-503973	19981015
			WO 1998-US21782	19981015
JP 2001519366	W		WO 1998-US21782	19981015
			JP 2000-515442	19981015
MX 2000003653	A1		MX 2000-3653	20000414
AU 751932	B		AU 1999-10893	19981015
US 2002183385	A1	Provisional	US 1997-62375P	19971015
			US 1998-173531	19981015

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9910893	A	Based on	WO 9918798
EP 1022951	A1	Based on	WO 9918798
BR 9813085	A	Based on	WO 9918798
NZ 503973	A	Based on	WO 9918798
JP 2001519366	W	Based on	WO 9918798
AU 751932	B	Previous Publ.	AU 9910893
		Based on	WO 9918798

PRIORITY APPLN. INFO: US 1997-62375P 19971015; US 1998-173531 19981015

AB WO 9918798 A UPAB: 20021105
NOVELTY - Solid tumors or metastatic neoplastic disease or hematopoietic disorders are treated by administration of one or more arsenic compounds (I).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(a) treatment of neoplastic diseases in humans comprising administration of (I) or its salt in combination with at least one other therapeutic agent;

(b) an oral pharmaceutical composition useful for treating neoplastic diseases in a human comprising (I) or its salt and a carrier, diluent or excipient; and

(c) a sterile unit dosage form adapted for parenteral administration comprising a non-lethal amount of arsenic trioxide in an aqueous carrier, the dosage form being contained in a **sealed** glass **container**.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - Phosphorous analogue able to interfere with signal transduction in apoptosis; inhibitor of angiogenesis.

USE - The method is particularly useful for treatment of tumors of the epithelial tissue, preferably epithelial glands, epithelial ducts,

liver, biliary tract, gastrointestinal tract, respiratory tract or urogenital tract, lymphoid tissue, connective tissue, bone or central nervous system, metastatic neoplastic diseases of the epithelial tissue, lymphoid tissue, connective tissue, bone or central nervous system. The tumor is preferably a squamous cell carcinoma of the esophagus, adenocarcinoma of esophagus, colorectal carcinoma, gastric carcinoma, Hodgkins lymphoma, non-Hodgkin's lymphoma, follicular lymphoma, diffuse lymphoma, lymphoblastic lymphoma, large cell lymphoma, small lymphocytic lymphoma, neuroblastoma, retinoblastoma, glioblastoma or oligodendroglioma (all claimed).

The compounds are also useful for the treatment of metastatic neoplastic diseases, e.g. primary and metastatic tumors of the central nervous system, refractory primary and metastatic tumors of the central nervous system, breast, lung, bladder and prostate cancer and refractory breast, lung, bladder and prostate cancer.

DESCRIPTION OF DRAWING(S) - The figure is a dose response curve for leukemic cell lines CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226 and SR after continuous exposure to 10-5 to 10-9 mu g/ml arsenic trioxide for 2 days.

Dwg.1a/4

L138 ANSWER 30 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-312193 [26] WPIDS
CROSS REFERENCE: 1996-259556 [26]; 1999-141873 [12]; 1999-141995 [12]; 1999-141996 [12]; 1999-302629 [25]; 2000-269088 [16]
DOC. NO. CPI: C1999-092089
TITLE: Composition for the treatment of cancer.
DERWENT CLASS: B05
INVENTOR(S): HARIDAS, K; HAUSHEER, F H; MURALI, D; PEDDAIAHGARI, S; REDDY, D G
PATENT ASSIGNEE(S): (BION-N) BIONUMERIK PHARM INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5902610	A	19990511	(199926)*		24

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5902610	A	CIP of	US 1994-338379	19941114
			US 1995-553005	19951103

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5902610	A	CIP of	US 5789000

PRIORITY APPLN. INFO: US 1995-553005 19951103; US 1994-338379 19941114

AB US 5902610 A UPAB: 20011211

NOVELTY - Composition comprising 2,2'-dithio-bis-ethane sulfonate (DBES), cis-diamine dichloro platinum (cisplatin), sodium chloride, and an **acid** selected from hydrochloric **acid** and phosphoric **acid**.

DETAILED DESCRIPTION - Composition comprising:

(a) 0.1-1.0 mg/ml DBES;

(b) 100-300 mg/ml cisplatin;

(c) 0.1-2.5 wt. % sodium chloride; and

(d) hydrochloric **acid** and/or phosphoric **acid**, in

amount to maintain the pH at 2.0-6.0.

An INDEPENDENT CLAIM is also included for reducing the toxic effects of cisplatin, by administration of DBES, or one of it's salts.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - None given.

USE - The composition is used for the treatment of cancer.

ADVANTAGE - The DBES reduces the toxicity, especially bone-marrow induced toxicity, in vivo associated with the use of cisplatin (claimed). The composition also exhibits synergistic activity.

DBES was administered at 1000 mg/kg to Fischer rats receiving a nephrotoxic dose of cisplatin (6 mg/kg). The composition gave 100 % protection against toxicity, as assessed by creatinine levels.

Dwg.0/5

L138 ANSWER 31 OF 31 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1994-199826 [24] WPIDS
CROSS REFERENCE: 1994-199827 [24]; 1994-199957 [24]
DOC. NO. CPI: C1994-091240
TITLE: Injectable antineoplastic **taxol** compsns. with improved stability - contain **taxol** in polyethoxylated castor oil adjusted to pH below 8.1.
DERWENT CLASS: A96 B02 P12 P33
INVENTOR(S): CARVER, D; ELLIOTT, R L; EWALD, H; HANDRECK, G P; PROUT, T; CARVER, D R; PROUT, T R; ELLIOTT, R; HANDRECK, P
PATENT ASSIGNEE(S): (FAUL-N) FAULDING & CO LTD F H; (FAUL-N) FAULDING F H & CO LTD; (NAPR-N) NAPRO BIOTHERAPEUTICS INC; (NAPR-N) NAPRO BIO THERAPEUTICS INC
COUNTRY COUNT: 45
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9412030	A1	19940609	(199424)*		9
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE					
W: AU BB BG BR CA CZ FI HU JP KP KR KZ LK MG MN MW NO NZ RO RU SD SK UA UZ					
AU 9351967	A	19940609	(199428)		
AU 9456126	A	19940622	(199436)		
ZA 9308844	A	19940928	(199440)		8
CN 1095266	A	19941123	(199546)		
NZ 258044	A	19951221	(199606)		
AU 667142	B	19960307	(199617)		
CN 1096673	A	19941228	(199719)		
EP 835657	A1	19980415	(199819)	EN	7
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
US 5733888	A	19980331	(199820)		4
ES 2119996	T3	19981016	(199849)		
US 5972992	A	19991026	(199952)		
US 5977164	A	19991102	(199953)		
CA 2308082	A1	19940609	(200048)	EN	
US 6140359	A	20001031	(200057)		
US 6306894	B1	20011023	(200165)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9412030	A1	WO 1993-US11199	19931118
AU 9351967	A	AU 1993-51967	19931125
AU 9456126	A	AU 1994-56126	19931118
ZA 9308844	A	ZA 1993-8844	19931126
CN 1095266	A	CN 1993-120529	19931127
NZ 258044	A	NZ 1993-258044	19931125

AU 667142	B		AU 1993-51967	19931125
CN 1096673	A		CN 1993-115293	19931126
EP 835657	A1	Div ex	EP 1994-901593	19931118
			EP 1997-121710	19931118
US 5733888	A	Cont of	US 1992-995501	19921222
			US 1996-594478	19960131
ES 2119996	T3		EP 1994-901593	19931118
US 5972992	A	Cont of	US 1992-995501	19921222
		Cont of	US 1996-594478	19960131
			US 1998-28906	19980224
US 5977164	A	Div ex	US 1996-594478	19960131
			US 1997-979836	19971126
CA 2308082	A1	Div ex	CA 1993-2149150	19931118
			CA 1993-2308082	19931118
US 6140359	A	Cont of	US 1992-995501	19921222
		Div ex	US 1996-594478	19960131
		Div ex	US 1997-979836	19971126
			US 1999-356158	19990719
US 6306894	B1	Cont of	US 1992-995501	19921222
		Div ex	US 1996-594478	19960131
		Cont of	US 1997-979836	19971126
		Cont of	US 1999-356158	19990719
			US 2000-563969	20000503

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9456126	A	Based on	WO 9412030
AU 667142	B	Previous Publ.	AU 9351967
EP 835657	A1	Div ex	EP 674510
ES 2119996	T3	Based on	EP 674510
US 5972992	A	Cont of	US 5733888
US 5977164	A	Div ex	US 5733888
US 6140359	A	Div ex	US 5733888
US 6306894	B1	Div ex	US 5733888
		Cont of	US 5977164
		Cont of	US 6140359

PRIORITY APPLN. INFO: US 1992-995501 19921222; AU 1992-6074 19921127

AB WO 9412030 A UPAB: 20011108

Compsn. consisting of **taxol** in a polyethoxylated castor oil has a pH less than 8.1

Acid is mixed with a polyethoxylated castor oil carrier material to form a first carrier soln. and then mixing **taxol** with this soln. to form a **taxol** soln. of pH less than 8.1. The **acid** is acetic **acid** or citric **acid**.

USE/ADVANTAGE - The injectable composition is antineoplastic with good cytotoxic activity against IP implanted D16 melanoma and the human X-1 mammary tumour xenograft. **Taxol** has good response rates in treating both ovarian and breast cancer patients who were not benefiting from vinca alkaloid or cisplatin therapy and has shown encouraging results in patients with other types of cancer including lung, melanoma, lymphoma, head and neck. The **taxol** composition has a lower pH than known formulations resulting in greater stability and longer shelf life than the known formulations. The **taxol** does not readily degrade.

In an example, a soln. was prepd. with the following formulation 0.5 ml Cremophor El, 2.0 mg citric **acid** (anhydrous), 6.0 mg **taxol**, and absolute alcohol to 1.0 ml. The pH of this soln. was 6.1. The stability of this sample was compared to that of a similar sample contg. no **acid** and of pH 9.1. The solns. were stored at 40 deg.C for 7 days in glass 5 ml **vials sealed** with rubber

bungs. After storage the pH of the 2 samples was 6.2 and 9.0, the potency was 96.6% and 86.7% the major individual impurity was 0.3% and 5.1% and the total impurities was 2.0% and 12.2%.
Dwg.0/0

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